Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water

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SUPPLEMENTARY MATERIAL

Trial Exhibit
Food & Water v. EPA
3:17-cv-02162-EMC
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Trial Ex. 131.008

Supplementary Material 1. Literature search for human and animal studies

This supplement documents the detailed search strategies across multiple bibliographic databases for human and animal studies published since Health Canada's 2010 monograph [1] and CADTH's 2019 review [2, 3], including grey literature search strategies, used in the present review. The supplement describes high-level search concepts and specific database search terms for Medline OVID, EMBASE, PubMed, CINAHL, Toxnet, PAIS Index, Human Technology Assessment, CENTRAL, Cochrane Library, and Clinical Trial Registries.

1.1. Strategy

Search Question	**Are there any health risks to exposure to fluoride in water?**		
Major Concepts	1. Fluoride/fluoridation 2. Water 3. Outcomes: cancer, bone/skeletal toxicity, developmental/reproductive toxicity, endocrine toxicity (including thyroid effects), immunotoxicity, genotoxicity and all other potential adverse effects		
Search Terms	**Concept 1**	**Concept 2**	**Concept 3**
	Fluorides, fluorine, flurine, fluride, fluoridation	Water, drinking water, tap water, well water, spring water, mineral water, carbonated water, community water, rivers, lakes, ponds, streams, water supply, water sources, water resources, water quality, water treatment	Adverse events, reactions, health risks, individual outcomes

1.2. Bibliographic database search terms and output

Medline Ovid [i]

Concept	#	Medline query
Fluoride	1	exp Fluorides/
	2	exp Fluoridation/
	3	fluorid*.tw.
	4	fluorin*.tw.
	5	flurin*.tw.
	6	flurid*.tw.
	7	or/1-6
Water	8	Water/
	9	water.tw.
	10	Drinking Water/
	11	drinking water.tw.
	12	exp Fresh Water/
	13	fresh water*.tw.
	14	freshwater*.tw.
	15	exp Mineral Waters/
	16	mineral water*.tw.
	17	exp Carbonated Water/
	18	carbonated water*.tw.
	19	exp Water Quality/
	20	(water adj3 quality).tw.
	21	exp Water Resources/
	22	(water* adj3 resource*).tw.
	23	Water Supply/
	24	(water adj3 supply).tw.
	25	(water* adj3 course*).tw.

[i] *MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present*

Concept	#	Medline query
	26	watercourse*.tw.
	27	exp Rivers/
	28	river*.tw.
	29	exp Lakes/
	30	lake*.tw.
	31	exp Ponds/
	32	pond*.tw.
	33	exp Groundwater/
	34	groundwater*.tw.
	35	ground water*.tw.
	36	Water Wells/
	37	water well*.tw.
	38	(water* adj3 course*).tw.
	39	watercourse*.tw.
	40	exp Natural Springs/
	41	natural spring*.tw.
	42	exp Hot Springs/
	43	hot spring*.tw.
	44	hotspring*.tw.
	45	spring water*.tw.
	46	springwater*.tw.
	47	(water* adj3 reservoir*).tw.
	48	stream*.tw.
	49	brook*.tw.
	50	creek*.tw.
	51	rivulet*.tw.
	52	rill*.tw.
	53	runnel*.tw.
	54	community water.tw.
	55	water fluoridation.tw.

Concept	#	Medline query
	56	community water fluoridation.tw.
	57	CWF.tw.
	58	or/8-57
Outcomes	59	exp Fluoride Poisoning/
	60	(fluoride adj3 poisoning).tw.
	61	exp Bone Diseases/
	62	cancer*.tw.
	63	exp Neoplasms/
	64	neoplas*.tw.
	65	malignan*.tw.
	66	tumor*.tw.
	67	tumour*.tw.
	68	sarcoma*.tw.
	69	carcinoma*.tw.
	70	tumor*.tw.
	71	(bone* adj3 disease*).tw.
	72	exp Bone Development/
	73	(bone* adj3 develop*).tw.
	74	exp Fractures, Bone/
	75	(bone* adj3 fracture*).tw.
	76	(bone* adj3 injur*).tw.
	77	(skelet* adj3 fluorosis).tw.
	78	(skelet* adj3 toxicit*).tw.
	79	exp Bone Neoplasms/
	80	(bone* adj3 cancer*).tw.
	81	(bone* adj3 neoplasm*).tw.
	82	(bone* adj3 tumor*).tw.
	83	(bone* adj3 tumour*).tw.
	84	(skelet* adj3 cancer*).tw.
	85	(skelet* adj3 neoplasm*).tw.

Concept	#	Medline query
	86	(skelet* adj3 tumor*).tw.
	87	(skelet* adj3 tumour*).tw.
	88	exp Endocrine System Diseases/
	89	(endocrin* adj3 diseas*).tw.
	90	(endocrin* adj3 disorder*).tw.
	91	(endocrin* adj3 disturbance*).tw.
	92	(endocrin* adj3 disruption*).tw.
	93	(endocrin* adj3 dysfunction*).tw.
	94	endocrinopath*.tw.
	95	(hormon* adj3 disease*).tw.
	96	(hormon* adj3 disorder*).tw.
	97	(hormon* adj3 disruption*).tw.
	98	(hormon* adj3 dysfunction*).tw.
	99	(hormon* adj3 imbalance*).tw.
	100	exp Thyroid Diseases/
	101	(thyroid* adj3 diseas*).tw.
	102	(thyroid* adj3 disorder*).tw.
	103	(thyroid* adj3 dysfunction*).tw.
	104	(thyroid* adj3 abnormalit*).tw.
	105	(thyroid* adj3 anomal*).tw.
	106	Neurodevelopmental Disorders/
	107	(neurodevelopment* adj3 disorder*).tw.
	108	(neurodevelopment* adj3 diseas*).tw.
	109	exp Developmental Disabilities/
	110	(development* adj3 disabilit*).tw.
	111	(development* adj3 dela*).tw.
	112	(development* adj3 abnormalit*).tw.
	113	Intellectual Disability/
	114	(intellectual adj3 disabilit*).tw.
	115	(intellectual adj3 dysfunction*).tw.

Concept	#	Medline query
	116	(intellectual adj3 impairment*).tw.
	117	exp Neurocognitive Disorders/
	118	neurocognitive disorder*.tw.
	119	exp cognition disorders/
	120	(cogniti* adj3 disorder*).tw.
	121	(cogniti* adj3 disease*).tw.
	122	exp Cognitive Dysfunction/
	123	(cogniti* adj3 dysfunction*).tw.
	124	Immune System Diseases/
	125	immunotoxic*.tw.
	126	immunopath*.tw.
	127	(immun* adj3 disease*).tw.
	128	(immun* adj3 disorder*).tw.
	129	(immun* adj3 dysfunction*).tw.
	130	(immun* adj3 dysregulation*).tw.
	131	Hypersensitivity/
	132	Hypersensitivity, Delayed/
	133	Hypersensitivity, Immediate/
	134	hypersensitivit*.tw.
	135	genotoxic*.tw.
	136	exp male urogenital diseases/
	137	exp Female Urogenital Diseases/
	138	(urogen* adj3 disease*).tw.
	139	(urogen* adj3 disorder*).tw.
	140	(genitourinary adj3 disease*).tw.
	141	(genitourinary adj3 disorder*).tw.
	142	(male adj3 genit*).tw.
	143	(female adj3 genit*).tw.
	144	(health adj3 hazard*).tw.
	145	(health adj3 risk*).tw.

Concept	#	Medline query
	146	or/59-145
Fluoride + water	147	7 and 58
Fluoride + water + outcomes	148	7 and 58 and 146
2016 - current	149	limit 148 to yr="2016 -Current"

EMBASE [ii]

Concept	#	EMBASE query
Fluoride	1	exp fluoride/
	2	exp fluoridation/
	3	fluorid*.tw.
	4	fluorin*.tw.
	5	flurin*.tw.
	6	flurid*.tw.
	7	or/1-6
Water	8	water/
	9	water.tw.
	10	drinking water/
	11	drinking water.tw.
	12	exp tap water/
	13	tap water.tw.
	14	tapwater.tw.
	15	exp fresh water/
	16	fresh water*.tw.
	17	freshwater*.tw.
	18	water quality/
	19	water quality.tw.
	20	water treatment/
	21	water treatment.tw.
	22	exp water supply/
	23	(water adj3 supply*).tw.
	24	(water* adj3 resource*).tw.
	25	(water* adj3 reservoir*).tw.
	26	(water* adj3 course*).tw.
	27	watercourse*.tw.

[ii] Embase: Excerpta Medica Database Guide

Concept	#	EMBASE query
	28	exp river/
	29	river*.tw.
	30	exp lake/
	31	lake*.tw.
	32	exp pond/
	33	pond*.tw.
	34	exp ground water/
	35	ground water*.tw.
	36	groundwater*.tw.
	37	exp well water/
	38	(water adj3 well*).tw.
	39	exp mineral water/
	40	mineral water*.tw.
	41	exp carbonated water/
	42	carbonated water*.tw.
	43	exp natural spring/
	44	natural spring*.tw.
	45	exp thermal spring/
	46	hot spring*.tw.
	47	hotspring*.tw.
	48	spring water*.tw.
	49	springwater*.tw.
	50	exp "stream (river)"/
	51	stream*.tw.
	52	brook*.tw.
	53	creek*.tw.
	54	rivulet*.tw.
	55	rill*.tw.
	56	runnel*.tw.
	57	community water.tw.

Concept	#	EMBASE query
	58	water fluoridation.tw.
	59	or/8-58
Outcomes	60	exp fluorosis/
	61	fluoride intoxication.tw.
	62	fluoride poisoning.tw.
	63	fluoridosis.tw.
	64	exp neoplasm/
	65	exp malignant neoplasm/
	66	neoplas*.tw.
	67	cancer*.tw.
	68	malignan*.tw.
	69	carcinoma*.tw.
	70	sarcoma*.tw.
	71	tumor*.tw.
	72	tumour*.tw.
	73	exp bone disease/
	74	(bone* adj3 diseas*).tw.
	75	(bone* adj3 disorder*).tw.
	76	(skelet* adj3 disease*).tw.
	77	(skelet* adj3 disorder*).tw.
	78	exp bone injury/
	79	(bone* adj3 injur*).tw.
	80	(bone* adj3 damage*).tw.
	81	(bone* adj3 fracture*).tw.
	82	(bone* adj3 trauma).tw.
	83	(skelet* adj3 injur*).tw.
	84	(skelet* adj3 damage*).tw.
	85	(skelet* adj3 fracture*).tw.
	86	(skelet* adj3 trauma).tw.
	87	exp bone development/

Concept	#	EMBASE query
	88	(bone* adj3 develop*).tw.
	89	osteogenesis.tw.
	90	(skelet* adj3 develop*).tw.
	91	skeletogenesis.tw.
	92	exp bone cancer/
	93	(bone* adj3 cancer*).tw.
	94	(bone* adj3 tumor*).tw.
	95	(bone* adj3 tumour*).tw.
	96	(bone* adj3 neoplasm*).tw.
	97	osteosarcoma*.tw.
	98	(skelet* adj3 cancer*).tw.
	99	(skelet* adj3 tumor*).tw.
	100	(skelet* adj3 tumour*).tw.
	101	(skelet* adj3 neoplasm*).tw.
	102	exp endocrine disease/
	103	(endocrin* adj3 disease*).tw.
	104	(endocrin* adj3 disorder*).tw.
	105	(endocrin* adj3 disturbance*).tw.
	106	(endocrin* adj3 dysfunction*).tw.
	107	(endocrin* adj3 disruption*).tw.
	108	endocrinopath*.tw.
	109	(hormon* adj3 disorder*).tw.
	110	(hormon* adj3 disruption*).tw.
	111	(hormon* adj3 dysfunction*).tw.
	112	(hormon* adj3 imbalance*).tw.
	113	thyroid disease/
	114	(thyroid* adj3 disease*).tw.
	115	(thyroid* adj3 disorder*).tw.
	116	(thyroid* adj3 abnormalit*).tw.
	117	(thyroid* adj3 anomal*).tw.

Concept	#	EMBASE query
	118	(thyroid* adj3 dysfunction*).tw.
	119	exp mental disease/
	120	(mental adj3 disease*).tw.
	121	(mental adj3 disorder*).tw.
	122	(mental adj3 disturbance*).tw.
	123	(mental adj3 illness*).tw.
	124	(neurodevelopment* adj3 disorder*).tw.
	125	(neuropsychiatric adj3 disorder*).tw.
	126	(psych* adj3 disease*).tw.
	127	(psych* adj3 disorder*).tw.
	128	(psych* adj3 disturbance*).tw.
	129	(psych* adj3 illness*).tw.
	130	exp developmental disorder/
	131	(development* adj3 disorder*).tw.
	132	(development* adj3 disease*).tw.
	133	(development* adj3 disabilit*).tw.
	134	(development* adj3 dela*).tw.
	135	(development* adj3 abnormalit*).tw.
	136	exp intellectual impairment/
	137	(intellectual adj3 impairment*).tw.
	138	(intellectual adj3 disabilit*).tw.
	139	(intellectual adj3 dysfunction*).tw.
	140	exp cognitive defect/
	141	(cogniti* adj3 defect*).tw.
	142	(cogniti* adj3 disorder*).tw.
	143	(cogniti* adj3 deficit*).tw.
	144	(cogniti* adj3 disabilit*).tw.
	145	(cogniti* adj3 impairment*).tw.
	146	(cogniti* adj3 dysfunction*).tw.
	147	exp immunopathology/

Concept	#	EMBASE query
	148	immunopath*.tw.
	149	(immun* adj3 disease*).tw.
	150	(immun* adj3 disorder*).tw.
	151	(immun* adj3 dysfunction*).tw.
	152	(immun* adj3 dysregulation*).tw.
	153	exp hypersensitivity/
	154	hypersensitivit*.tw.
	155	exp genotoxicity/
	156	genotoxic*.tw.
	157	exp urogenital tract disease/
	158	(urogenital adj3 disease*).tw.
	159	(urogenital adj3 disorder*).tw.
	160	(genitourinary adj3 disease*).tw.
	161	(genitourinary adj3 disorder*).tw.
	162	(male adj3 genit*).tw.
	163	(female adj3 genit*).tw.
	164	exp health hazard/
	165	(health adj3 hazard*).tw.
	166	(health adj3 risk*).tw.
	167	or/60-166
Fluoride + water	168	7 and 59
Fluoride + water + outcomes	169	7 and 59 and 167
2016 - current	170	limit 169 to yr="2016 -Current"

PubMed

Concept	#	Pubmed Query
Fluoride	1	fluoride[MeSH Terms]
	2	fluoridation[MeSH Terms]
	3	fluorid*[Text Word]
	4	fluorin*[Text Word]
	5	flurin*[Text Word]
	6	flurid*[Text Word]
	7	(((((((fluoride[MeSH Terms]) OR fluoridation[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word]) OR flurid*[Text Word])))
Water	8	water[MeSH Terms]
	9	water[Text Word]
	10	drinking water[MeSH Terms]
	11	drinking water[Text Word]
	12	tap water[MeSH Terms]
	13	tap water[Text Word]
	14	fresh water[MeSH Terms]
	15	fresh water*[Text Word]
	16	freshwater*[Text Word]
	17	water quality[MeSH Terms]
	18	water qualit*[Text Word]
	19	water treatment[MeSH Terms]
	20	water treatment*[Text Word]
	21	water supply[MeSH Terms]
	22	water supply[Text Word]
	23	water resource[MeSH Terms]
	24	water resource*[Text Word]
	25	water reservoir*[Text Word]
	26	water course[Text Word]

Concept	#	Pubmed Query
	27	watercourse*[Text Word]
	28	river[MeSH Terms]
	29	river*[Text Word]
	30	lake[MeSH Terms]
	31	lake*[Text Word]
	32	pond[MeSH Terms]
	33	pond*[Text Word]
	34	ground water[MeSH Terms]
	35	ground water*[Text Word]
	36	groundwater*[Text Word]
	37	water well[MeSH Terms]
	38	water well*[Text Word]
	39	mineral water[MeSH Terms]
	40	mineral water*[Text Word]
	41	carbonated water[MeSH Terms]
	42	carbonated water*[Text Word]
	43	natural spring[MeSH Terms]
	44	natural spring*[Text Word]
	45	thermal spring*[Text Word]
	46	hot spring[MeSH Terms]
	47	hot spring*[Text Word]
	48	hotspring*[Text Word]
	49	spring water[MeSH Terms]
	50	spring water*[Text Word]
	51	springwater*[Text Word]
	52	stream[MeSH Terms]
	53	stream*[Text Word]
	54	brook*[Text Word]
	55	creek*[Text Word]

Concept	#	Pubmed Query
	56	rivulet*[Text Word]
	57	rill*[Text Word]
	58	runnel*[Text Word]
	59	community water[MeSH Terms]
	60	community water*[Text Word]
	61	community water fluoridation[MeSH Terms]
	62	water fluoridation*[Text Word]
	63	community water fluoridation[Text Word]
	64	((water[MeSH Terms]) OR water[Text Word]) OR drinking water[MeSH Terms]) OR drinking water[Text Word]) OR tap water[MeSH Terms]) OR tap water[Text Word]) OR fresh water[MeSH Terms]) OR fresh water*[Text Word]) OR freshwater*[Text Word]) OR water quality[MeSH Terms]) OR water qualit*[Text Word]) OR water treatment[MeSH Terms]) OR water treatment*[Text Word]) OR water supply[MeSH Terms]) OR water supply[Text Word]) OR water resource[MeSH Terms]) OR water resource*[Text Word]) OR water reservoir*[Text Word]) OR water course[Text Word]) OR watercourse*[Text Word]) OR river[MeSH Terms]) OR river*[Text Word]) OR lake[MeSH Terms]) OR lake*[Text Word]) OR pond[MeSH Terms]) OR pond*[Text Word]) OR ground water[MeSH Terms]) OR ground water*[Text Word]) OR groundwater*[Text Word]) OR water well[MeSH Terms]) OR water well*[Text Word]) OR mineral water[MeSH Terms]) OR mineral water*[Text Word]) OR carbonated water[MeSH Terms]) OR carbonated water*[Text Word]) OR natural spring[MeSH Terms]) OR natural spring*[Text Word]) OR thermal spring*[Text Word]) OR hot spring[MeSH Terms]) OR hot spring*[Text Word]) OR hotspring*[Text Word]) OR spring water[MeSH Terms]) OR spring water*[Text Word]) OR springwater*[Text Word]) OR stream[MeSH Terms]) OR stream*[Text Word]) OR brook*[Text Word]) OR

Concept	#	Pubmed Query
		creek*[Text Word]) OR rivulet*[Text Word]) OR rill*[Text Word]) OR runnel*[Text Word]) OR community water[MeSH Terms]) OR community water*[Text Word]) OR community water fluoridation[MeSH Terms]) OR community water fluoridation[Text Word]) OR water fluoridation*[Text Word]
Outcomes	65	((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumor[MeSH Terms]) OR tumor*[Text Word]) OR tumour[MeSH Terms]) OR tumour*[Text Word])) OR ((((((((((((((((((((((((((((((((bone disease[MeSH Terms]) OR bone disease*[Text Word]) OR bone disorder*[Text Word]) OR bone injur*[Text Word]) OR bone fracture[MeSH Terms]) OR bone* fracture*[Text Word]) OR bone* trauma*[Text Word]) OR bone* damage*[Text Word]) OR skelet* disease*[Text Word]) OR skelet* disorder*[Text Word]) OR skelet* injur*[Text Word]) OR skelet* fracture*[Text Word]) OR skelet* trauma*[Text Word]) OR skelet* damage*[Text Word]) OR bone neoplasm[MeSH Terms]) OR bone* neoplas*[Text Word]) OR bone cancer[MeSH Terms]) OR bone* cancer*[Text Word]) OR bone* tumor*[Text Word]) OR bone* tumour*[Text Word]) OR osteosarcoma[MeSH Terms]) OR osteosarcoma*[Text Word]) OR skelet* neoplas*[Text Word]) OR skelet* cancer*[Text Word]) OR skelet* tumor*[Text Word]) OR skelet* tumour*[Text Word]) OR bone development[MeSH Terms]) OR bone* development[Text Word]) OR osteogenesis[MeSH Terms]) OR osteogenesis[Text Word]) OR skelet* development[Text Word]) OR skeletogenesis[Text Word])) OR ((((((((((((((((((((endocrine disease[MeSH Terms]) OR endocrin* disease*[Text Word]) OR endocrin* disorder*[Text Word]) OR

Concept	#	Pubmed Query
		endocrin disturbance*[Text Word]) OR endocrin* disruption*[Text Word]) OR endocrin* dysfunction*[Text Word]) OR endocrinopath*[Text Word]) OR hormon* disease*[Text Word]) OR hormon* disorder*[Text Word]) OR hormon* disturbance*[Text Word]) OR hormon* disruption*[Text Word]) OR hormon* dysfunction*[Text Word]) OR hormon* imbalance*[Text Word]) OR thyroid disease[MeSH Terms]) OR thyroid* disease*[Text Word]) OR thyroid dysgenesis[MeSH Terms]) OR thyroid* dysgenesis[Text Word]) OR thyroid* disorder*[Text Word]) OR thyroid* abnormal*[Text Word]) OR thyroid* anomal*[Text Word]) OR thyroid* dysfunction*[Text Word])) OR ((((((((((((((((((((((((((((((((mental disorders[MeSH Terms]) OR mental disorder*[Text Word]) OR mental disease*[Text Word]) OR mental disturbance*[Text Word]) OR mental illness*[Text Word]) OR neurodevelopment* disease*[Text Word]) OR neurodevelopment* disorder*[Text Word]) OR neurodevelopment* disabilit*[Text Word]) OR neurodevelopment* dela*[Text Word]) OR ((developmental disorder, speech or language[MeSH Terms]))) OR developmental disorders of scholastic skills[MeSH Terms]) OR development* disorder*[Text Word]) OR developmental disability[MeSH Terms]) OR development* disabilit*[Text Word]) OR developmental delay disorder[MeSH Terms]) OR development* dela*[Text Word]) OR development* abnormalit*[Text Word]) OR development* impairment*[Text Word]) OR intellectual disability[MeSH Terms]) OR intellectual* disabilit*[Text Word]) OR aphasia, intellectual[MeSH Terms]) OR intellectual aphasia*[Text Word]) OR intellectual impairment*[Text Word]) OR intellectual dysfunction*[Text Word]) OR delirium, dementia, amnestic, cognitive disorders[MeSH Terms]) OR cognition disorders[MeSH Terms]) OR cognit* disorder*[Text Word]) OR mild cognitive impairment[MeSH Terms]) OR cogniti*

Concept	#	Pubmed Query
		impair*[Text Word]) OR cogniti* disease*[Text Word]) OR cogniti* defect*[Text Word]) OR cogniti* deficit*[Text Word]) OR cogniti* disabilit*[Text Word]) OR cogniti* dysfunction*[Text Word])) OR ((((((((((((((((((((immunologic disease[MeSH Terms]) OR immunologic* disease*[Text Word]) OR immunologic* disorder*[Text Word]) OR immunologic* dysfunction*[Text Word]) OR immunologic* dysregulat*[Text Word]) OR immediate hypersensitivity[MeSH Terms]) OR delayed hypersensitivity[MeSH Terms]) OR hypersensitivit*[Text Word]) OR immunopath*[Text Word]) OR genotoxic*[Text Word]) OR male urogenital disease[MeSH Terms]) OR female urogenital disease[MeSH Terms]) OR urogenit* disease*[Text Word]) OR urogenit* disorder*[Text Word]) OR male genitourinary disease[MeSH Terms]) OR female genitourinary disease[MeSH Terms]) OR genitourin* disease*[Text Word]) OR genitourin* disorder*[Text Word]) OR health risk appraisal[MeSH Terms]) OR health risk*[Text Word]) OR health hazard*[Text Word]))))
Fl + water	66	((((((((((fluoride[MeSH Terms]) OR fluoridation[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word]) OR flurid*[Text Word])))))) AND ((water[MeSH Terms]) OR water[Text Word]) OR drinking water[MeSH Terms]) OR drinking water[Text Word]) OR tap water[MeSH Terms]) OR tap water[Text Word]) OR fresh water[MeSH Terms]) OR fresh water*[Text Word]) OR freshwater*[Text Word]) OR water quality[MeSH Terms]) OR water qualit*[Text Word]) OR water treatment[MeSH Terms]) OR water treatment*[Text Word]) OR water supply[MeSH Terms]) OR water supply[Text Word]) OR water resource[MeSH Terms]) OR water resource*[Text Word]) OR water reservoir*[Text Word]) OR water course[Text Word]) OR watercourse*[Text Word]) OR

Concept	#	Pubmed Query
		river[MeSH Terms]) OR river*[Text Word]) OR lake[MeSH Terms]) OR lake*[Text Word]) OR pond[MeSH Terms]) OR pond*[Text Word]) OR ground water[MeSH Terms]) OR ground water*[Text Word]) OR groundwater*[Text Word]) OR water well[MeSH Terms]) OR water well*[Text Word]) OR mineral water[MeSH Terms]) OR mineral water*[Text Word]) OR carbonated water[MeSH Terms]) OR carbonated water*[Text Word]) OR natural spring[MeSH Terms]) OR natural spring*[Text Word]) OR thermal spring*[Text Word]) OR hot spring[MeSH Terms]) OR hot spring*[Text Word]) OR hotspring*[Text Word]) OR spring water[MeSH Terms]) OR spring water*[Text Word]) OR springwater*[Text Word]) OR stream[MeSH Terms]) OR stream*[Text Word]) OR brook*[Text Word]) OR creek*[Text Word]) OR rivulet*[Text Word]) OR rill*[Text Word]) OR runnel*[Text Word]) OR community water[MeSH Terms]) OR community water*[Text Word]) OR community water fluoridation[MeSH Terms]) OR community water fluoridation[Text Word]) OR water fluoridation*[Text Word]))
Fl + water + outcomes	67	((((((((((fluoride[MeSH Terms]) OR fluoridation[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word]) OR flurid*[Text Word])))))) AND ((water[MeSH Terms]) OR water[Text Word]) OR drinking water[MeSH Terms]) OR drinking water[Text Word]) OR tap water[MeSH Terms]) OR tap water[Text Word]) OR fresh water[MeSH Terms]) OR fresh water*[Text Word]) OR freshwater*[Text Word]) OR water quality[MeSH Terms]) OR water qualit*[Text Word]) OR water treatment[MeSH Terms]) OR water treatment*[Text Word]) OR water supply[MeSH Terms]) OR water supply[Text Word]) OR water resource[MeSH Terms]) OR water resource*[Text Word]) OR water reservoir*[Text Word]) OR water course[Text Word]) OR watercourse*[Text Word]) OR

Concept	#	Pubmed Query
		river[MeSH Terms]) OR river*[Text Word]) OR lake[MeSH Terms]) OR lake*[Text Word]) OR pond[MeSH Terms]) OR pond*[Text Word]) OR ground water[MeSH Terms]) OR ground water*[Text Word]) OR groundwater*[Text Word]) OR water well[MeSH Terms]) OR water well*[Text Word]) OR mineral water[MeSH Terms]) OR mineral water*[Text Word]) OR carbonated water[MeSH Terms]) OR carbonated water*[Text Word]) OR natural spring[MeSH Terms]) OR natural spring*[Text Word]) OR thermal spring*[Text Word]) OR hot spring[MeSH Terms]) OR hot spring*[Text Word]) OR hotspring*[Text Word]) OR spring water[MeSH Terms]) OR spring water*[Text Word]) OR springwater*[Text Word]) OR stream[MeSH Terms]) OR stream*[Text Word]) OR brook*[Text Word]) OR creek*[Text Word]) OR rivulet*[Text Word]) OR rill*[Text Word]) OR runnel*[Text Word]) OR community water[MeSH Terms]) OR community water*[Text Word]) OR community water fluoridation[MeSH Terms]) OR community water fluoridation[Text Word]) OR water fluoridation*[Text Word]))) AND ((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumor[MeSH Terms]) OR tumor*[Text Word]) OR tumour[MeSH Terms]) OR tumour*[Text Word])) OR ((((((((((((((((((((((((((((((((bone disease[MeSH Terms]) OR bone disease*[Text Word]) OR bone disorder*[Text Word]) OR bone injur*[Text Word]) OR bone fracture[MeSH Terms]) OR bone* fracture*[Text Word]) OR bone* trauma*[Text Word]) OR bone* damage*[Text Word]) OR skelet* disease*[Text Word]) OR skelet* disorder*[Text Word]) OR skelet* injur*[Text Word]) OR skelet* fracture*[Text Word]) OR skelet*

Concept	#	Pubmed Query
		trauma*[Text Word]) OR skelet* damage*[Text Word]) OR bone neoplasm[MeSH Terms]) OR bone* neoplas*[Text Word]) OR bone cancer[MeSH Terms]) OR bone* cancer*[Text Word]) OR bone* tumor*[Text Word]) OR bone* tumour*[Text Word]) OR osteosarcoma[MeSH Terms]) OR osteosarcoma*[Text Word]) OR skelet* neoplas*[Text Word]) OR skelet* cancer*[Text Word]) OR skelet* tumor*[Text Word]) OR skelet* tumour*[Text Word]) OR bone development[MeSH Terms]) OR bone* development[Text Word]) OR osteogenesis[MeSH Terms]) OR osteogenesis[Text Word]) OR skelet* development[Text Word]) OR skeletogenesis[Text Word])) OR ((((((((((((((((((((endocrine disease[MeSH Terms]) OR endocrin* disease*[Text Word]) OR endocrin* disorder*[Text Word]) OR endocrin disturbance*[Text Word]) OR endocrin* disruption*[Text Word]) OR endocrin* dysfunction*[Text Word]) OR endocrinopath*[Text Word]) OR hormon* disease*[Text Word]) OR hormon* disorder*[Text Word]) OR hormon* disturbance*[Text Word]) OR hormon* disruption*[Text Word]) OR hormon* dysfunction*[Text Word]) OR hormon* imbalance*[Text Word]) OR thyroid disease[MeSH Terms]) OR thyroid* disease*[Text Word]) OR thyroid dysgenesis[MeSH Terms]) OR thyroid* dysgenesis[Text Word]) OR thyroid* disorder*[Text Word]) OR thyroid* abnormal*[Text Word]) OR thyroid* anomal*[Text Word]) OR thyroid* dysfunction*[Text Word])) OR ((((((((((((((((((((((((((((((((mental disorders[MeSH Terms]) OR mental disorder*[Text Word]) OR mental disease*[Text Word]) OR mental disturbance*[Text Word]) OR mental illness*[Text Word]) OR neurodevelopment* disease*[Text Word]) OR neurodevelopment* disorder*[Text Word]) OR neurodevelopment* disabilit*[Text Word]) OR neurodevelopment* dela*[Text Word]) OR ((developmental disorder, speech or language[MeSH Terms]))) OR developmental disorders of

Concept	#	Pubmed Query
		scholastic skills[MeSH Terms]) OR development* disorder*[Text Word]) OR developmental disability[MeSH Terms]) OR development* disabilit*[Text Word]) OR developmental delay disorder[MeSH Terms]) OR development* dela*[Text Word]) OR development* abnormalit*[Text Word]) OR development* impairment*[Text Word]) OR intellectual disability[MeSH Terms]) OR intellectual* disabilit*[Text Word]) OR aphasia, intellectual[MeSH Terms]) OR intellectual aphasia*[Text Word]) OR intellectual impairment*[Text Word]) OR intellectual dysfunction*[Text Word]) OR delirium, dementia, amnestic, cognitive disorders[MeSH Terms]) OR cognition disorders[MeSH Terms]) OR cognit* disorder*[Text Word]) OR mild cognitive impairment[MeSH Terms]) OR cogniti* impair*[Text Word]) OR cogniti* disease*[Text Word]) OR cogniti* defect*[Text Word]) OR cogniti* deficit*[Text Word]) OR cogniti* disabilit*[Text Word]) OR cogniti* dysfunction*[Text Word])) OR ((((((((((((((((((((immunologic disease[MeSH Terms]) OR immunologic* disease*[Text Word]) OR immunologic* disorder*[Text Word]) OR immunologic* dysfunction*[Text Word]) OR immunologic* dysregulat*[Text Word]) OR immediate hypersensitivity[MeSH Terms]) OR delayed hypersensitivity[MeSH Terms]) OR hypersensitivit*[Text Word]) OR immunopath*[Text Word]) OR genotoxic*[Text Word]) OR male urogenital disease[MeSH Terms]) OR female urogenital disease[MeSH Terms]) OR urogenit* disease*[Text Word]) OR urogenit* disorder*[Text Word]) OR male genitourinary disease[MeSH Terms]) OR female genitourinary disease[MeSH Terms]) OR genitourin* disease*[Text Word]) OR genitourin* disorder*[Text Word]) OR health risk appraisal[MeSH Terms]) OR health risk*[Text Word]) OR health hazard*[Text Word])))))

Concept	#	Pubmed Query
2016 - current	68	Search ((((((((((((fluoride[MeSH Terms]) OR fluoridation[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word]) OR flurid*[Text Word])))))) AND ((water[MeSH Terms]) OR water[Text Word]) OR drinking water[MeSH Terms]) OR drinking water[Text Word]) OR tap water[MeSH Terms]) OR tap water[Text Word]) OR fresh water[MeSH Terms]) OR fresh water*[Text Word]) OR freshwater*[Text Word]) OR water quality[MeSH Terms]) OR water qualit*[Text Word]) OR water treatment[MeSH Terms]) OR water treatment*[Text Word]) OR water supply[MeSH Terms]) OR water supply[Text Word]) OR water resource[MeSH Terms]) OR water resource*[Text Word]) OR water reservoir*[Text Word]) OR water course[Text Word]) OR watercourse*[Text Word]) OR river[MeSH Terms]) OR river*[Text Word]) OR lake[MeSH Terms]) OR lake*[Text Word]) OR pond[MeSH Terms]) OR pond*[Text Word]) OR ground water[MeSH Terms]) OR ground water*[Text Word]) OR groundwater*[Text Word]) OR water well[MeSH Terms]) OR water well*[Text Word]) OR mineral water[MeSH Terms]) OR mineral water*[Text Word]) OR carbonated water[MeSH Terms]) OR carbonated water*[Text Word]) OR natural spring[MeSH Terms]) OR natural spring*[Text Word]) OR thermal spring*[Text Word]) OR hot spring[MeSH Terms]) OR hot spring*[Text Word]) OR hotspring*[Text Word]) OR spring water[MeSH Terms]) OR spring water*[Text Word]) OR springwater*[Text Word]) OR stream[MeSH Terms]) OR stream*[Text Word]) OR brook*[Text Word]) OR creek*[Text Word]) OR rivulet*[Text Word]) OR rill*[Text Word]) OR runnel*[Text Word]) OR community water[MeSH Terms]) OR community water*[Text Word]) OR community water fluoridation[MeSH Terms]) OR community water fluoridation[Text Word]) OR water fluoridation*[Text Word]))) AND

Concept	#	Pubmed Query
		((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumor[MeSH Terms]) OR tumor*[Text Word]) OR tumour[MeSH Terms]) OR tumour*[Text Word])) OR ((((((((((((((((((((((((((((((((bone disease[MeSH Terms]) OR bone disease*[Text Word]) OR bone disorder*[Text Word]) OR bone injur*[Text Word]) OR bone fracture[MeSH Terms]) OR bone* fracture*[Text Word]) OR bone* trauma*[Text Word]) OR bone* damage*[Text Word]) OR skelet* disease*[Text Word]) OR skelet* disorder*[Text Word]) OR skelet* injur*[Text Word]) OR skelet* fracture*[Text Word]) OR skelet* trauma*[Text Word]) OR skelet* damage*[Text Word]) OR bone neoplasm[MeSH Terms]) OR bone* neoplas*[Text Word]) OR bone cancer[MeSH Terms]) OR bone* cancer*[Text Word]) OR bone* tumor*[Text Word]) OR bone* tumour*[Text Word]) OR osteosarcoma[MeSH Terms]) OR osteosarcoma*[Text Word]) OR skelet* neoplas*[Text Word]) OR skelet* cancer*[Text Word]) OR skelet* tumor*[Text Word]) OR skelet* tumour*[Text Word]) OR bone development[MeSH Terms]) OR bone* development[Text Word]) OR osteogenesis[MeSH Terms]) OR osteogenesis[Text Word]) OR skelet* development[Text Word]) OR skeletogenesis[Text Word])) OR ((((((((((((((((((endocrine disease[MeSH Terms]) OR endocrin* disease*[Text Word]) OR endocrin* disorder*[Text Word]) OR endocrin disturbance*[Text Word]) OR endocrin* disruption*[Text Word]) OR endocrin* dysfunction*[Text Word]) OR endocrinopath*[Text Word]) OR hormon* disease*[Text Word]) OR hormon* disorder*[Text Word]) OR hormon* disturbance*[Text Word]) OR hormon* disruption*[Text Word]) OR hormon*

Concept	#	Pubmed Query
		dysfunction*[Text Word]) OR hormon* imbalance*[Text Word]) OR thyroid disease[MeSH Terms]) OR thyroid* disease*[Text Word]) OR thyroid dysgenesis[MeSH Terms]) OR thyroid* dysgenesis[Text Word]) OR thyroid* disorder*[Text Word]) OR thyroid* abnormal*[Text Word]) OR thyroid* anomal*[Text Word]) OR thyroid* dysfunction*[Text Word])) OR ((((((((((((((((((((((((((((((mental disorders[MeSH Terms]) OR mental disorder*[Text Word]) OR mental disease*[Text Word]) OR mental disturbance*[Text Word]) OR mental illness*[Text Word]) OR neurodevelopment* disease*[Text Word]) OR neurodevelopment* disorder*[Text Word]) OR neurodevelopment* disabilit*[Text Word]) OR neurodevelopment* dela*[Text Word]) OR ((developmental disorder, speech or language[MeSH Terms]))) OR developmental disorders of scholastic skills[MeSH Terms]) OR development* disorder*[Text Word]) OR developmental disability[MeSH Terms]) OR development* disabilit*[Text Word]) OR developmental delay disorder[MeSH Terms]) OR development* dela*[Text Word]) OR development* abnormalit*[Text Word]) OR development* impairment*[Text Word]) OR intellectual disability[MeSH Terms]) OR intellectual* disabilit*[Text Word]) OR aphasia, intellectual[MeSH Terms]) OR intellectual aphasia*[Text Word]) OR intellectual impairment*[Text Word]) OR intellectual dysfunction*[Text Word]) OR delirium, dementia, amnestic, cognitive disorders[MeSH Terms]) OR cognition disorders[MeSH Terms]) OR cognit* disorder*[Text Word]) OR mild cognitive impairment[MeSH Terms]) OR cogniti* impair*[Text Word]) OR cogniti* disease*[Text Word]) OR cogniti* defect*[Text Word]) OR cogniti* deficit*[Text Word]) OR cogniti* disabilit*[Text Word]) OR cogniti* dysfunction*[Text Word])) OR ((((((((((((((((((((immunologic disease[MeSH Terms]) OR immunologic* disease*[Text Word]) OR immunologic* disorder*[Text

Concept	#	Pubmed Query
		Word]) OR immunologic* dysfunction*[Text Word]) OR immunologic* dysregulat*[Text Word]) OR immediate hypersensitivity[MeSH Terms]) OR delayed hypersensitivity[MeSH Terms]) OR hypersensitivit*[Text Word]) OR immunopath*[Text Word]) OR genotoxic*[Text Word]) OR male urogenital disease[MeSH Terms]) OR female urogenital disease[MeSH Terms]) OR urogenit* disease*[Text Word]) OR urogenit* disorder*[Text Word]) OR male genitourinary disease[MeSH Terms]) OR female genitourinary disease[MeSH Terms]) OR genitourin* disease*[Text Word]) OR genitourin* disorder*[Text Word]) OR health risk appraisal[MeSH Terms]) OR health risk*[Text Word]) OR health hazard*[Text Word])))))) AND ("2016"[Date - Publication] : "2020"[Date - Publication])

CINAHL [iii]

Concept	#	Cinahl query
Fluoride	1	fluoride
	2	fluoride in water
	3	water fluoridation or fluoridation of water or fluoride treatment or fluoride in water
	4	fluoridation or fluoride or fluoridated
	5	TX water fluorid* OR TX fluorid* OR TX fluorin* OR TX flurin* OR TX flurid*
	6	S1 OR S2 OR S3 OR S4 OR S5
Water	7	drinking water OR tap water
	8	TX drinking water OR TX tap water

[iii] Cumulative Index to Nursing and Allied Health Literature

Concept	#	Cinahl query
	9	drinking water quality OR drinking water treatment OR drinking water safety
	10	TX drinking water quality OR TX drinking water treatment OR TX drinking water safety
	11	ground water OR water wells OR river OR lake OR pond
	12	TX ground water OR TX water wells OR TX river OR TX lake OR TX pond
	13	mineral water OR carbonated water OR spring water OR hot springs
	14	TX mineral water OR TX carbonated water OR TX spring water OR TX hot springs
	15	S7 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
Outcomes	16	fluorosis
	17	fluoride toxicity
	18	bone disease
	19	TX bone* disease*
	20	bone disorder
	21	TX bone* disorder*
	22	skeletal disease
	23	TX skelet* disease*
	24	skeletal disorders
	25	TX skelet* disorder*
	26	bone injury
	27	TX bone* injur*
	28	bone fracture
	29	TX bone* fracture*
	30	TX bone* damage*
	31	bone trauma
	32	TX bone* trauma*
	33	TX skelet* injur*

Concept	#	Cinahl query
	34	TX skelet* damage*
	35	TX skelet* fracture*
	36	skeletal trauma
	37	TX skelet* trauma*
	38	bone development
	39	TX bone* development*
	40	osteogenesis
	41	TX osteogen*
	42	TX skelet* develop*
	43	TX skeletogen*
	44	bone cancer
	45	TX bone* cancer*
	46	bone tumor
	47	TX bone* tumor*
	48	TX bone* tumour*
	49	bone neoplasm
	50	TX bone* neoplas*
	51	osteosarcoma
	52	TX osteosarcoma*
	53	osteogenic sarcoma
	54	TX osteogenic sarcoma*
	55	TX skelet* cancer*
	56	TX skelet* tumor*
	57	TX skelet* tumour*
	58	TX skelet* neoplas*
	59	endocrine disease
	60	TX endocrin* disease*
	61	endocrine disorders
	62	TX endocrin* disorder*
	63	endocrine disruptors

Concept	#	Cinahl query
	64	endocrine disrupting chemicals
	65	TX endocrin* disrupt*
	66	TX endocrin* disturbance*
	67	TX endocrin* dysfunction*
	68	endocrine pathology
	69	TX endocrin* patholo*
	70	TX endocrinopath*
	71	TX hormon* disease*
	72	hormone disorders
	73	TX hormon* disorder*
	74	hormone disruptor
	75	TX hormon* disruptor*
	76	hormone imbalance
	77	TX hormon* imbalance*
	78	TX hormon* dysfunction*
	79	thyroid disease
	80	TX thyroid* disease*
	81	thyroid disorders
	82	TX thyroid* disorder*
	83	thyroid cancer
	84	TX thyroid* cancer*
	85	thyroid neoplasms
	86	TX thyroid* neoplas*
	87	thyroid adenoma
	88	TX thyroid* adenoma*
	89	TX thyroid* abnormalit*
	90	TX thyroid* anomal*
	91	thyroid dysfunction
	92	TX thyroid* dysfunction*
	93	water fluoridation cancer

Concept	#	Cinahl query
	94	mental disease
	95	TX mental* disease*
	96	mental disorders
	97	TX mental* disorder*
	98	mental illness
	99	TX mental* illness*
	100	mental disabilities
	101	TX mental* disabilit*
	102	mental disturbance
	103	TX mental* disturbance*
	104	psychiatric disease
	105	TX psych* disease*
	106	psychiatric disorders
	107	TX psych* disorder*
	108	psychiatric illness
	109	TX psych* illness*
	110	TX psych* disturbance*
	111	TX deveopment* disease*
	112	developmental disorders
	113	TX development* disorder*
	114	developmental disabilities
	115	TX development* disabilit*
	116	developmental delay
	117	TX development* dela*
	118	TX development* abnormalit*
	119	intellectual disability
	120	TX intellectual disabilit*
	121	intellectual impairment
	122	TX intellectual impairment*
	123	TX intellectual dysfunction*

Concept	#	Cinahl query
	124	cognitive disease
	125	TX cogniti* disease*
	126	cognitive disorders
	127	TX cogniti* disorder*
	128	TX cogniti* defect*
	129	cognitive deficits
	130	TX cogniti* deficit*
	131	cognitive disabilities
	132	TX cogniti* disabilit*
	133	cognitive impairment
	134	TX cogniti* impairment*
	135	cognitive dysfunction
	136	TX cogniti* dysfunction*
	137	TX cogniti* dysregulation*
	138	immune disease
	139	TX immun* disease*
	140	immune disorders
	141	TX immun* disorder*
	142	immune dysfunction
	143	TX immun* dysfunction*
	144	immune dysregulation
	145	TX immun* dysregulation*
	146	immunopathogenesis
	147	TX immunopath*
	148	hypersensitivity
	149	TX hypersensitiv*
	150	genotoxicity
	151	genotoxic
	152	TX genotoxic*
	153	TX urogenital disease*

Concept	#	Cinahl query
	154	urogenital disorder
	155	TX urogenital disorder*
	156	urogenital dysfunction
	157	TX urogenital dysfunction*
	158	TX genitourinary disease*
	159	TX genitourinary disorder*
	160	TX genitourinary dysfunction
	161	male genitalia
	162	TX male* genit*
	163	female genitalia
	164	TX female* genit*
	165	health hazards
	166	TX health hazard*
	167	health risks
	168	TX health risk*
	169	cancer
	170	TX cancer*
	171	neoplasm
	172	TX neoplas*
	173	malignancy
	174	malignant
	175	TX malignan*
	176	tumor
	177	TX tumor*
	178	tumour
	179	TX tumour*
	180	carcinoma
	181	TX carcino*
	182	sarcoma
	183	TX sarcoma*

Concept	#	Cinahl query
	184	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153 OR S154 OR S155 OR S156 OR S157 OR S158 OR S159 OR S160 OR S161 OR S162 OR S163 OR S164 OR S165 OR S166 OR S167 OR S168 OR S169 OR S170 OR S171 OR S172 OR S173 OR S174 OR S175 OR S176 OR S177 OR S178 OR S179 OR S180 OR S181 OR S182 OR S183 OR S184S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61

Concept	#	Cinahl query
		OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 ...Show Less
	185	DT 2016 OR DT 2017 OR DT 2018 OR DT 2019 OR DT 2020
	186	S6 AND S15
	187	S6 AND S15 AND S184
	188	S6 AND S15 AND S184 AND S185

Toxnet [iv]

Concept	#	Query
Fl	1	(((((((fluoride[MeSH Terms]) OR fluoridation[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word]) OR flurid*[Text Word])))
Water	2	((water[MeSH Terms]) OR water[Text Word]) OR drinking water[MeSH Terms]) OR drinking water[Text Word]) OR tap water[MeSH Terms]) OR tap water[Text Word]) OR fresh water[MeSH Terms]) OR fresh water*[Text Word]) OR freshwater*[Text Word]) OR water quality[MeSH Terms]) OR water qualit*[Text Word]) OR water treatment[MeSH Terms]) OR

[iv] The toxicology literature database for the National Institutes of Health, USA

Concept	#	Query
		water treatment*[Text Word]) OR water supply[MeSH Terms]) OR water supply[Text Word]) OR water resource[MeSH Terms]) OR water resource*[Text Word]) OR water reservoir*[Text Word]) OR water course[Text Word]) OR watercourse*[Text Word]) OR river[MeSH Terms]) OR river*[Text Word]) OR lake[MeSH Terms]) OR lake*[Text Word]) OR pond[MeSH Terms]) OR pond*[Text Word]) OR ground water[MeSH Terms]) OR ground water*[Text Word]) OR groundwater*[Text Word]) OR water well[MeSH Terms]) OR water well*[Text Word]) OR mineral water[MeSH Terms]) OR mineral water*[Text Word]) OR carbonated water[MeSH Terms]) OR carbonated water*[Text Word]) OR natural spring[MeSH Terms]) OR natural spring*[Text Word]) OR thermal spring*[Text Word]) OR hot spring[MeSH Terms]) OR hot spring*[Text Word]) OR hotspring*[Text Word]) OR spring water[MeSH Terms]) OR spring water*[Text Word]) OR springwater*[Text Word]) OR stream[MeSH Terms]) OR stream*[Text Word]) OR brook*[Text Word]) OR creek*[Text Word]) OR rivulet*[Text Word]) OR rill*[Text Word]) OR runnel*[Text Word]) OR community water[MeSH Terms]) OR community water*[Text Word]) OR community water fluoridation[MeSH Terms]) OR community water fluoridation[Text Word]) OR water fluoridation*[Text Word]
Outcomes	3	((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumor[MeSH Terms]) OR tumor*[Text Word]) OR tumour[MeSH Terms]) OR tumour*[Text Word])) OR ((((((((((((((((((((((((((((((((bone disease[MeSH Terms]) OR bone disease*[Text Word]) OR bone disorder*[Text Word]) OR bone injur*[Text Word]) OR bone

Concept	#	Query
		fracture[MeSH Terms]) OR bone* fracture*[Text Word]) OR bone* trauma*[Text Word]) OR bone* damage*[Text Word]) OR skelet* disease*[Text Word]) OR skelet* disorder*[Text Word]) OR skelet* injur*[Text Word]) OR skelet* fracture*[Text Word]) OR skelet* trauma*[Text Word]) OR skelet* damage*[Text Word]) OR bone neoplasm[MeSH Terms]) OR bone* neoplas*[Text Word]) OR bone cancer[MeSH Terms]) OR bone* cancer*[Text Word]) OR bone* tumor*[Text Word]) OR bone* tumour*[Text Word]) OR osteosarcoma[MeSH Terms]) OR osteosarcoma*[Text Word]) OR skelet* neoplas*[Text Word]) OR skelet* cancer*[Text Word]) OR skelet* tumor*[Text Word]) OR skelet* tumour*[Text Word]) OR bone development[MeSH Terms]) OR bone* development[Text Word]) OR osteogenesis[MeSH Terms]) OR osteogenesis[Text Word]) OR skelet* development[Text Word]) OR skeletogenesis[Text Word])) OR ((((((((((((((((((((endocrine disease[MeSH Terms]) OR endocrin* disease*[Text Word]) OR endocrin* disorder*[Text Word]) OR endocrin disturbance*[Text Word]) OR endocrin* disruption*[Text Word]) OR endocrin* dysfunction*[Text Word]) OR endocrinopath*[Text Word]) OR hormon* disease*[Text Word]) OR hormon* disorder*[Text Word]) OR hormon* disturbance*[Text Word]) OR hormon* disruption*[Text Word]) OR hormon* dysfunction*[Text Word]) OR hormon* imbalance*[Text Word]) OR thyroid disease[MeSH Terms]) OR thyroid* disease*[Text Word]) OR thyroid dysgenesis[MeSH Terms]) OR thyroid* dysgenesis[Text Word]) OR thyroid* disorder*[Text Word]) OR thyroid* abnormal*[Text Word]) OR thyroid* anomal*[Text Word]) OR thyroid* dysfunction*[Text Word])) OR ((((((((((((((((((((((((((((((((((((mental disorders[MeSH Terms]) OR mental disorder*[Text Word]) OR mental disease*[Text Word]) OR mental disturbance*[Text Word]) OR mental illness*[Text Word]) OR neurodevelopment*

Concept	#	Query
		disease*[Text Word]) OR neurodevelopment* disorder*[Text Word]) OR neurodevelopment* disabilit*[Text Word]) OR neurodevelopment* dela*[Text Word]) OR ((developmental disorder, speech or language[MeSH Terms])) OR developmental disorders of scholastic skills[MeSH Terms]) OR development* disorder*[Text Word]) OR developmental disability[MeSH Terms]) OR development* disabilit*[Text Word]) OR developmental delay disorder[MeSH Terms]) OR development* dela*[Text Word]) OR development* abnormalit*[Text Word]) OR development* impairment*[Text Word]) OR intellectual disability[MeSH Terms]) OR intellectual* disabilit*[Text Word]) OR aphasia, intellectual[MeSH Terms]) OR intellectual aphasia*[Text Word]) OR intellectual impairment*[Text Word]) OR intellectual dysfunction*[Text Word]) OR delirium, dementia, amnestic, cognitive disorders[MeSH Terms]) OR cognition disorders[MeSH Terms]) OR cognit* disorder*[Text Word]) OR mild cognitive impairment[MeSH Terms]) OR cogniti* impair*[Text Word]) OR cogniti* disease*[Text Word]) OR cogniti* defect*[Text Word]) OR cogniti* deficit*[Text Word]) OR cogniti* disabilit*[Text Word]) OR cogniti* dysfunction*[Text Word])) OR ((((((((((((((((((((immunologic disease[MeSH Terms]) OR immunologic* disease*[Text Word]) OR immunologic* disorder*[Text Word]) OR immunologic* dysfunction*[Text Word]) OR immunologic* dysregulat*[Text Word]) OR immediate hypersensitivity[MeSH Terms]) OR delayed hypersensitivity[MeSH Terms]) OR hypersensitivit*[Text Word]) OR immunopath*[Text Word]) OR genotoxic*[Text Word]) OR male urogenital disease[MeSH Terms]) OR female urogenital disease[MeSH Terms]) OR urogenit* disease*[Text Word]) OR urogenit* disorder*[Text Word]) OR male genitourinary disease[MeSH Terms]) OR female genitourinary disease[MeSH Terms]) OR genitourin* disease*[Text Word]) OR

Concept	#	Query
		genitourin* disorder*[Text Word]) OR health risk appraisal[MeSH Terms]) OR health risk*[Text Word]) OR health hazard*[Text Word]))))
Toxicology	4	tox [subset]
Fl + water	5	1 AND 2
Fl + water + outcomes	6	1 AND 2 AND 3
Fl + water + outcomes (toxicology)	7	1 AND 2 AND 3 AND 4
2016-current		limit 7 to yr="2016 -Current"

PAIS Index

Concept	#	PAIS query
Fluoride	1	su(fluoride) OR su(Fluorides) OR su(fluoridation) OR su(fluoridation of water) OR su(fluoridation of drinking water)
Water	2	su(Water) OR su(tap water) OR su(drinking water) OR su(tap water and drinking water) OR su(Water Quality) OR su(water safety) OR su(water treatment)
	3	su(Ground Water) OR su(water wells) OR su(Rivers) OR su(Lakes) OR su(Ponds) OR su(Water Sources)

Concept	#	PAIS query
	4	su(mineral water) OR su(carbonated water) OR su(spring water) OR su(Hot Springs)
	5	(su(Water) OR su(tap water) OR su(drinking water) OR su(tap water AND drinking water) OR su(Water Quality) OR su(water safety) OR su(water treatment)) OR (su(Ground Water) OR su(water wells) OR su(Rivers) OR su(Lakes) OR su(Ponds) OR su(Water Sources)) OR (su(mineral water) OR su(carbonated water) OR su(spring water) OR su(Hot Springs))
Fluoride + water	6	(su(fluoride) OR su(Fluorides) OR su(fluoridation) OR su(fluoridation of water) OR su(fluoridation of drinking water)) AND ((su(Water) OR su(tap water) OR su(drinking water) OR su(tap water AND drinking water) OR su(Water Quality) OR su(water safety) OR su(water treatment)) OR (su(Ground Water) OR su(water wells) OR su(Rivers) OR su(Lakes) OR su(Ponds) OR su(Water Sources)) OR (su(mineral water) OR su(carbonated water) OR su(spring water) OR su(Hot Springs)))

Health Technology Assessment

Concept	#	Medline query
Fluoride	1	exp Fluorides/
	2	exp Fluoridation/
	3	fluorid*.tw.
	4	fluorin*.tw.
	5	flurin*.tw.
	6	flurid*.tw.
	7	or/1-6

Water	8	exp Water/
	9	drinking water.tw.
	10	tap water*.tw.
	11	exp water supply/
	12	(water* adj3 suppl*).tw.
	13	(water* adj3 treatment*).tw.
	14	exp Water Purification/
	15	(water* adj3 purification).tw.
	16	lake*.tw.
	17	pond*.tw.
	18	ground water*.tw.
	19	exp mineral waters/
	20	mineral water*.tw.
	21	hot spring*.tw.
	22	communit* water*.tw.
	23	or/8-22
Fluoride + water	24	7 and 23

Cochrane Database of Systematic Reviews (CDSR)

Concept	#	CDSR query
Fluoride	1	fluoride.mp. [mp=title, abstract, full text, keywords, caption text]
	2	fluoridation.mp. [mp=title, abstract, full text, keywords, caption text]
	3	fluorin*.mp. [mp=title, abstract, full text, keywords, caption text]
	4	flurin*.mp. [mp=title, abstract, full text, keywords, caption text]
	5	flurid*.mp. [mp=title, abstract, full text, keywords, caption text]
	6	or/1-5
Water	7	water.mp. [mp=title, abstract, full text, keywords, caption text]
	8	drinking water.mp. [mp=title, abstract, full text, keywords, caption text]
	9	tap water.mp. [mp=title, abstract, full text, keywords, caption text]
	10	(water adj3 fluorid*).mp. [mp=title, abstract, full text, keywords, caption text]
	11	community water*.mp. [mp=title, abstract, full text, keywords, caption text]
	12	fresh water.mp. [mp=title, abstract, full text, keywords, caption text]
	13	freshwater.mp. [mp=title, abstract, full text, keywords, caption text]
	14	ground water.mp. [mp=title, abstract, full text, keywords, caption text]
	15	groundwater.mp. [mp=title, abstract, full text, keywords, caption text]
	16	(water* adj3 well*).mp. [mp=title, abstract, full text, keywords, caption text]
	17	mineral water*.mp. [mp=title, abstract, full text, keywords, caption text]

Concept	#	CDSR query
	18	carbonated water*.mp. [mp=title, abstract, full text, keywords, caption text]
	19	spring water*.mp. [mp=title, abstract, full text, keywords, caption text]
	20	(water* adj3 resource*).mp. [mp=title, abstract, full text, keywords, caption text]
	21	(water* adj3 source*).mp. [mp=title, abstract, full text, keywords, caption text]
	22	(water* adj3 suppl*).mp. [mp=title, abstract, full text, keywords, caption text]
	23	river*.mp. [mp=title, abstract, full text, keywords, caption text]
	24	lake*.mp. [mp=title, abstract, full text, keywords, caption text]
	25	pond*.mp. [mp=title, abstract, full text, keywords, caption text]
	26	or/7-25
Fluoride + water	27	6 and 26
2016 - current	28	limit 27 to last 5 years

Cochrane Central Register of Controlled Trials (CENTRAL)

Concept	#	CENTRAL query
Fluoride	1	exp fluorides/
	2	exp Fluoridation/
	3	fluorid*.tw.
	4	fluorin*.tw.
	5	flurin*.tw.
	6	flurid*.tw.
	7	or/1-6
Water	8	water/
	9	exp Drinking Water/
	10	drinking water.tw.
	11	tap water.tw.
	12	tapwater.tw.
	13	exp Water Quality/
	14	(water adj3 quality).tw.
	15	community water.tw.
	16	water fluoridation.tw.
	17	exp groundwater/
	18	groundwater*.tw.
	19	ground water*.tw.
	20	exp Water Wells/
	21	(water* adj3 well*).tw.
	22	exp Natural Springs/
	23	natural spring*.tw.
	24	hot spring*.tw.
	25	springwater.tw.
	26	spring water*.tw.
	27	exp Mineral Waters/
	28	minteral water*.tw.
	29	exp Carbonated Water/

Concept	#	CENTRAL query
	30	carbonated water*.tw.
	31	exp fresh water/
	32	fresh water*.tw.
	33	freshwater*.tw.
	34	exp Lakes/
	35	lake*.tw.
	36	exp Ponds/
	37	pond*.tw.
	38	exp Rivers/
	39	river*.tw.
	40	exp water supply/
	41	(water* adj3 suppl*).tw.
	42	or/8-41
Fluoride + water	43	7 and 42
2016 - current	44	limit 43 to yr="2016 -Current"

Cochrane Library (Wiley)

Concept	#	Cochrane query
Fluoride	1	MeSH descriptor: [Fluorides] in all MeSH products
	2	MeSH descriptor: [Fluoridation] explode all trees
	3	(fluorid*):ti,ab,kw
	4	#1 OR #2 OR #3
Water	5	MeSH descriptor: [Drinking Water] explode all trees
	6	MeSH descriptor: [Water Quality] explode all trees
	7	#5 OR #6
Outcomes	8	MeSH descriptor: [Bone Development] explode all trees
	9	MeSH descriptor: [Bone Diseases] explode all trees
	10	MeSH descriptor: [Fractures, Bone] explode all trees
	11	MeSH descriptor: [Bone Neoplasms] explode all trees
	12	MeSH descriptor: [Osteosarcoma] explode all trees
	13	MeSH descriptor: [Endocrine System Diseases] explode all trees
	14	MeSH descriptor: [Endocrine Disruptors] explode all trees
	15	MeSH descriptor: [Thyroid Diseases] explode all trees
	16	MeSH descriptor: [Thyroid Dysgenesis] explode all trees
	17	MeSH descriptor: [Thyroid Neoplasms] explode all trees
	18	MeSH descriptor: [Neurodevelopmental Disorders] explode all trees
	19	MeSH descriptor: [Learning Disorders] explode all trees
	20	MeSH descriptor: [Agnosia] explode all trees
	21	MeSH descriptor: [Agraphia] explode all trees
	23	MeSH descriptor: [Aphasia] explode all trees
	24	MeSH descriptor: [Intellectual Disability] explode all trees
	25	MeSH descriptor: [Neurocognitive Disorders] explode all trees
	26	MeSH descriptor: [Cognitive Dysfunction] explode all trees
	27	MeSH descriptor: [Immune System Diseases] explode all trees
	28	MeSH descriptor: [Hypersensitivity] explode all trees
	29	MeSH descriptor: [Genital Diseases, Male] explode all trees

Concept	#	Cochrane query
	30	MeSH descriptor: [Genital Neoplasms, Male] explode all trees
	31	MeSH descriptor: [Genitalia, Male] explode all trees
	32	MeSH descriptor: [Genital Diseases, Female] explode all trees
	33	MeSH descriptor: [Genital Neoplasms, Female] explode all trees
	34	MeSH descriptor: [Genitalia, Female] explode all trees
	35	MeSH descriptor: [Male Urogenital Diseases] explode all trees
	36	MeSH descriptor: [Female Urogenital Diseases] explode all trees
	37	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
	38	#4 AND #7
	39	#4 AND #7 AND # 37

Clinical Trial Registries

Trial Database	Comment
World Health Organization	Completed trials, with results
European Union	Completed trials, with results
ISRCTN	Completed trials, with results
US Clinical Trials	Completed trials, with results
UK Clinical Trials gateway	
Health Canada	Ongoing trials, no results available

1.3. Grey literature

Resource	Strategy
Agency for Healthcare Research and Quality (AHRQ)	Fluoride
CAB Direct	Fl, water and outcomes
North American Agency for Drugs and Technologies in Health (CADTH)	Fluoride
North American Public Documents Collection	Fluoride (title or abstract)
Centers for Disease Control and Prevention (CDC)	
Centre for Reviews and Dissemination (CRD)	Fluoride
Conference Board E-Library	Fluoride
Environmental Protection Agency (EPA)	
Grey Literature Publishers List - International (The New York Academy of Medicine)	Fluoride (title or summary)
Grey literature Report	Fluoride
Health Quality Ontario	Fluoride
Health Systems Evidence	Fluoride
National Cancer Institute	
National Institute for Health and Care Excellence (NICE)	Fluoride
National Library of Medicine (MedlinePlus)	Fluoride
National Institutes of Health	
TRIP Database	Fluoride and water
World Catalogue (Worldcat)	Fluoride and water

Supplementary Material 2. Included human studies

This supplement expands on tables of epidemiologic studies included in the present review presented in the main manuscript . Lists of all included studies are provided, according to health endpoint. For each included study, comprehensive study characteristics and results are described. A description of the OHAT risk of bias assessment for each eligible study is provided.

The 89 included original studies examined a wide range of adverse health effects due to exposure to fluoride in water, particularly dental fluorosis (33 studies) and neurocognitive (28 studies), bone and skeletal (9 studies), and endocrine and urogenital outcomes (8 studies, each). The following table provides a summary of all identified fluoride-related adverse health outcomes. Studies were arranged in a descending chronological order then alphabetically by main author's last name.

2.1. Included human studies, by endpoint

Study	Dental	Cancer	Bone / Skeletal	Neuro/ Cognitive	Development/ Reproductive	Endocrine	Urogenital	Cardio-vascular	Hepatic	Geno-toxicity	Others
Abstracts	**N= 0**	**N= 0**	**N= 0**	**N= 1**	**N= 1**	**N= 0**	**N= 0**	**N= 0**	**N= 0**	**N= 0**	**N= 0**
Chauhan 2017 [4]					✓						
Stephenson 2017 [5]				✓							
Original Studies	**N= 33**	**N= 4**	**N= 9**	**N= 28**	**N= 5**	**N= 8**	**N= 8**	**N= 4**	**N= 2**	**N= 3**	**N= 6**
Mercado 2023 [6]	✓										
Tang 2023 [7]	✓										
Ahmad 2022 [8]				✓							

Study	Dental	Cancer	Bone / Skeletal	Neuro/ Cognitive	Development/ Reproductive	Endocrine	Urogenital	Cardio-vascular	Hepatic	Geno-toxicity	Others
Feng 2022 [9]				✓							
García-Escobar 2022 [10]	✓										
Goodman 2022 [11]				✓							
Gupta 2022 [12]	✓										
Ibarluzea 2022 [13]				✓							
Kaur 2022 [14]				✓							
Marques 2022 [15]	✓										
McLaren 2022 [16]	✓										
Rani 2022 [17]	✓										
Saeed 2022 [18]	✓			✓							
Tawfik 2022 [19]	✓										
Thilakarathne 2022 [20]	✓										
Al-Omoush 2021 [21]	✓										
Ayele 2021 [22]			✓	✓				✓			GIT, fatigue
Cao 2021 [23]	✓										
Dong 2021 [24]	✓										
Du 2021 [25]						✓					
Farmus 2021 [26]	✓										
Fernandes 2021 [27]	✓										

Study	Dental	Cancer	Bone / Skeletal	Neuro/ Cognitive	Development/ Reproductive	Endocrine	Urogenital	Cardio-vascular	Hepatic	Geno-toxicity	Others
Helte 2021 [28]			✓								
James 2021 [29]	✓										
Meghe 2021 [30]			✓								
Meng 2021 [31]										✓	
Mohd Nor 2021 [32]	✓										
Rojanaworarit 2021 [33]	✓										
Sharma 2021 [34]	✓		✓								Non-skeletal manifestations of fluoride toxicity
Silva 2021 [35]	✓										
Tkachenko 2021 [36]								✓			
Wang 2021 [37]	✓			✓							
Yani 2021 [38]	✓			✓							
Yu 2021 [39]	✓										
Zhao 2021 [40]	✓										
Bai 2020 [41]					✓						
Cui 2020 [42]				✓		✓					
Das 2020 [43]	✓										
Fernandes 2020 [44]	✓										
Godebo 2020 [45]			✓								

Study	Dental	Cancer	Bone / Skeletal	Neuro/ Cognitive	Development/ Reproductive	Endocrine	Urogenital	Cardio-vascular	Hepatic	Geno-toxicity	Others
Kim 2020 [46]		✓									
Krishna 2020 [47]						✓					
Lee 2020 [48]		✓	✓								
Nanayakkara 2020 [49]							✓				
Russ 2020 [50]				✓							
Stangvaltaite-Mouhat 2020 [51]	✓										
Sun 2020 [52]			✓								
Till 2020 [53]				✓							
Wang 2020 [54]				✓		✓					
An 2019 [55]					✓						
Crnosija 2019 [56]		✓									
Fernando 2019 [57]							✓				
Jimenez-Cordova 2019 [58]							✓	✓			
Jimenez-Cordova 2019a [59]											Arsenic metabolism
Khanoranga 2019 [60]		✓									
Liu 2019 [61]					✓						
Malin 2019 [62]							✓		✓		
Malin 2019a [63]				✓							
Pei 2019 [64]		✓	✓							✓	

Study	Dental	Cancer	Bone / Skeletal	Neuro/ Cognitive	Development/ Reproductive	Endocrine	Urogenital	Cardio-vascular	Hepatic	Geno-toxicity	Others
Riddell 2019 [65]				✓							
Shaik 2019 [66]						✓					
Soto-barreras 2019 [67]		✓									
Zhang 2019 [68]					✓						
Zhou 2019 [69]											Select eye diseases
Zhou 2019a [70]	✓										
Bashash 2018 [71]				✓							
Cui 2018 [72]				✓							
Jimenez-Cordova 2018 [73]							✓				
Kumar, V 2018 [74]						✓					
Kumar, S 2018 [75]	✓										
Malin 2018 [76]						✓					
Mohd Nor 2018 [77]	✓										
Mustafa 2018 [78]				✓							
Oweis 2018 [79]			✓								
Quadri 2018 [80]							✓				
Rathore 2018 [81]						✓					
Shruthi 2018 [82]											Non-skeletal manifestations of fluoride toxicity
Yu 2018 [83]				✓							

Study	Dental	Cancer	Bone / Skeletal	Neuro/ Cognitive	Development/ Reproductive	Endocrine	Urogenital	Cardio-vascular	Hepatic	Geno-toxicity	Others
Arulkumar 2017 [84]				✓				✓	✓		
Bashash 2017 [85]				✓							
Verma 2017 [86]	✓										
Cardenas-Gonzalez 2016 [87]							✓				
de Moura 2016 [88]	✓										
Heck 2016 [89]				✓							General health, trouble working
Kousik 2016 [90]				✓	✓						
Sabokseir 2016 [91]	✓										
Xiang 2016 [92]	✓										

Trial Ex. 131.063

2.2. Characteristics of the included human studies

Data abstraction and risk of bias assessment - human studies

(Studies arranged in a descending chronological order then alphabetically by author's last name)

Mercado 2023 [6]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Peru **Participants:** 12-15 years old students **Sampling time frame:** 2012 **Sample size:** 504	**Exposures:** Fluoride levels in: • Ground water **Method of exposure assessment:** • SPANDS method	**Outcome(s):** • Dental fluorosis	**Statistical analysis:** • Descriptive analysis **Results:** Fluoride in water/Dean's fluorosis index: Panchacutes I: 0.98mg/L/2.08 Tiabaya Pampas Nuevas: 0.79 mg/L/1.90	"The higher concentration of fluoride in drinking water is directly related to the higher degree of fluorosis."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: Girls: 34.52% **Exclusions:** • Students with an oral pathology treatment • Live in a different region of the school **Source of funding / support:** NR **Author declaration of interest:** NR	**Exposure level(s):** • Ground water (mg/L) 0.22-0.98 mg/L	**Method of outcome ascertainment:** • Dean's index	Tiabaya El Cural: 0.73 mg/L/1.72 La Bedoya: 0.43 mg/L/1.54 Panchacutes II: 0.32 mg/L/1.42 La Tomialla: 0.22 mg/L/1.26 Dental fluorosis for Panchacutes I: Severe: 10.71% Moderate: 23.81% Mild: 32.14% Very Mild: 26.19% Questionable: 7.143 % Normal: 0% Tiabaya Pampas Nuevas: Severe: 8.33% Moderate: 21.43% Mild: 30.95% Very Mild: 26.19% Questionable: 9.52 % Normal: 3.57% Tiabaya "El Cural": Severe: 5.95% Moderate: 19.05% Mild: 29.76% Very Mild: 26.19%	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Questionable: 10.71 % Normal: 8.33% <u>La Bedoya:</u> Severe: 3.57% Moderate: 15.48% Mild: 29.76% Very Mild: 27.38% Questionable: 13.10 % Normal: 10.71% <u>Panchacutes II:</u> Severe: 2.38% Moderate: 13.10% Mild: 28.57% Very Mild: 28.57% Questionable: 15.48 % Normal: 11.90% <u>La Tomialla:</u> Severe: 0% Moderate: 10.71% Mild: 27.38% Very Mild: 30.95% Questionable: 16.69% Normal: 14.29 % Relationship between fluoridation and DF: ($p<0,05$; $\chi 2<0,05$)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Relationship between “Never” Fluoridation and DF Normal: 7.5% Questionable: 12.5% Very Mild: 27.5% Mild: 30% Moderate: 17.5% Severe: 5% Relationship between “One” Fluoridation and DF Normal: 8.26% Questionable: 11.98% Very Mild: 27.69% Mild: 29.75% Moderate: 17.36% Severe: 4.96% Relationship between “Two” Fluoridation and DF Normal: 8.14% Questionable: 12.21% Very Mild: 27.33% Mild: 29.65% Moderate: 17.44% Severe: 5.23%	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Relationship between “Three” Fluoridation and DF Normal: 8.0% Questionable: 12.0% Very Mild: 28.0% Mild: 30.0% Moderate: 16.0% Severe: 6.0%	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe, according to the same criteria and from the same eligible population.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (students with an oral pathology treatment, and those who live in a different region than the school's one).
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from water wells and the local schools, using the SPANDS method.
	Can we be confident in the outcome assessment?	++	Yes, DF was assessed by researchers who were evaluated by university professor, using Dean's fluorosis index. Blinding of exposure status may have not significantly biased the assessment.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Tang 2023 [7]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** 7-14 years old children residing since birth in study area that is supplied by groundwater **Sampling time frame:** NR **Sample size:** 593	**Exposures:** Fluoride levels in: • Ground water • Urine samples **Method of exposure assessment:** • Fluoride in Drinking water and Urine samples: Ion-selective potentiometry (PF-202-CF; INESA Scientific Instrument Co., Ltd., China)	**Outcome(s):** • Dental fluorosis	**Statistical analysis:** • Descriptive analysis • Mediation analysis • Adjusted for age, sex, BMI, parental education, family income and low birth weight, in addition to urinary creatinine for urine fluoride assessments **Results:** • Water fluoride concentration >1mg/L and DF prevalence: Normal: 17 (5.6%) Very mild: 47 (15.5%) Mild: 210 (69.3%) Moderate:29(9.6%) • Water fluoride concentration 1mg/L and DF prevalence: Normal: 216 (74.5%) Very mild: 22 (15.2%) Mild: 30 (10.3%)	• Since “stratified analysis indicated a weaker association between fluoride concentration and DF prevalence in boys than in girls.”, “the DF prevalence may be sex-specific.” • Inflammatory factors may partially mediate the increased prevalence of mild DF in school-aged children with low-to-moderate fluoride exposure. • The study demonstrates that the risk of DF has

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: N (%): Girls: 300 (50.6%) **Exclusions:** • History of chronic medical conditions or other endemic diseases, such as kidney, liver, or endocrine disorders • Children living in areas with exposure to other pollutants, such as lead, arsenic, or mercury. **Source of funding / support:** • National Natural Science Foundation of China (Grants No. 82073515, and No. 81773388) • The State Key Program of National Natural Science Foundation of China	**Exposure level(s):** (Chinese standard fluoride limit in water = 1.0mg/L) • Water fluoride: 0.20 to 3.90, mean 1.42 (SD 1.00), median 1.20 (IQR 0.70–2.20) mg/L • Urinary fluoride: 0.01 to 5.54, mean 1.36 (SD 1.31), median 0.56 (IQR 0.16-2.29) mg/L • Fluoride concentration.: Mea ± SD (>1mg/L): Higher exposure gp.: Water: 2.19 ±0.81 Urine: 2.48 ±0.88 Lower exposure gp.:	**Method of outcome ascertainment:** • Dean's Index	Moderate:0(0.00%) • Water fluoride and DF (*PR* (95% *CI*), increase per 1ml/L): Overall DF: 1.50 (1.42, 1.57) Very mild DF: 1.85 (1.64, 2.07) Moderate DF: 3.92 (3.03, 5.06) *P* < 0.001 • Urinary fluoride DF (*PR* (95% *CI*), increase per 1ml/L): Overall DF: 1.42 (1.35, 1.50) Very mild DF: 1.67 (1.48, 1.88) Mild DF:1.72 (1.61, 1.84) moderate DF: 3.02 (2.50, 4.13) P < 0.001 Association between fluoride content and DF by sex: PR (95%CI) *Water Fluoride* Overall: 1.33 (1.29, 1.36),	an upward trend when the fluoride gradually in increases, in water and urine.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
(Grant No. 81430076) **Author declaration of interest:** No COI	Water: 0.61 ±0.24 Urine: 0.18 ±0.12		P-interaction=0.325 Very Mild: 1.31 (1.23, 1.39) P-interaction=0.485 Mild: 1.39 (1.35, 1.44) P-interaction=0.431 Moderate: 1.33 (1.25, 1.42) P-interaction=0.852 *Urinary Fluoride:* Overall: 1.27 (1.23, 1.30) P-interaction=0.013 Very Mild: 1.25 (1.17, 1.32) P-interaction=0.025 Mild: 1.32 (1.28, 1.36) P-interaction=0.014 Moderate: 1.27 (1.20, 1.36) P-interaction=0.170 <u>Sensitivity analysis for effect of fluoride exposure on DF: [PR (95%CI) for every 1mg/L increment of water fluoride]</u> *Adjusted for age and sex, water fluoride (mg/L)* Overall: 1.50 (1.42, 1.57) WHO Guideline: 0.78 (0.66, 0.89) * Very Mild: 1.83 (1.62, 2.06) WHO Guideline: 1.25 (0.98, 1.52) *	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Mild: 1.72 (1.61, 1.83) WHO Guideline: 1.10 (0.93, 1.27) * Moderate: 3.18 (2.54, 3.98) WHO Guideline: 3.13 (2.35, 3.90) * *Adjusted for BMI, water fluoride (mg/L)* Overall: 1.50 (1.42, 1.58) WHO Guideline: 0.79 (0.67, 0.91) * Very Mild: 1.82 (1.62, 2.05) WHO Guideline: 1.23 (0.95, 1.51) * Mild: 1.72 (1.61, 1.83) WHO Guideline: 1.11 (0.94, 1.28) * Moderate: 3.27 (2.73, 3.92) WHO Guideline: 3.15 (2.40, 3.90) * *Adjusted for parental education, and family income, water fluoride (mg/L)* Overall: 1.50 (1.43, 1.58) WHO Guideline: 0.79 (0.67, 0.91) * Very Mild: 1.83 (1.63, 2.06)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			WHO Guideline: 1.22 (0.95, 1.50) * Mild: 1.73 (1.62, 1.84) WHO Guideline: 1.11 (0.94,1.28) * Moderate: 3.78 (2.93, 4.88) WHO Guideline: 3.12 (2.29, 3.95) * *Adjusted for low birth weight, water fluoride (mg/L)* Overall: 1.50 (1.42, 1.57) WHO Guideline: 0.79 (0.67, 0.91) * Very Mild: 1.83 (1.62, 2.06) WHO Guideline: 1.21 (0.92, 1.50) * Mild: 1.72 (1.61, 1.83) WHO Guideline: 1.11 (0.94, 1.28) * Moderate: 3.384 (2.82, 4.07) WHO Guideline: 3.13 (2.37, 3.89) * *Adjusted for age, sex, BMI, parental education, family income, and low birth weight, water fluoride (mg/L)* Overall: 1.50 (1.42, 1.58)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			WHO Guideline: 0.78 (0.66, 0.90) * Very Mild: 1.85 (1.64, 2.07) WHO Guideline: 1.24 (0.95, 1.52) * Mild: 1.723 (1.61, 1.84) WHO Guideline: 1.10 (0.93,1.27) * Moderate: 3.92 (3.03, 5.06) WHO Guideline: 3.13 (2.32, 3.94) * *Water fluoride ≤ 1.5 is reference. P=0.001 <u>Sensitivity analysis for effect of fluoride exposure on DF: [PR (95%CI) for every 1mg/L increment of urinary fluoride]</u> *Adjusted for age and sex, urinary fluoride (mg/L)* Overall: 1.41 (1.34, 1.48) Very Mild: 1.66 (1.48, 1.87) Mild: 1.57 (1.48, 1.68) Moderate: 2.68 (2.26, 3.19) *Adjusted for BMI, urinary fluoride (mg/L)* Overall: 1.41 (1.34, 1.48) Very Mild: 1.63 (1.44, 1.85) Mild: 1.57 (1.47, 1.67)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Moderate: 2.59 (2.18, 3.08) *Adjusted for parental education, and family income, urinary fluoride (mg/L)* Overall: 1.41 (1.34, 1.48) Very Mild: 1.65 (1.47, 1.85) Mild: 1.57 (1.47, 1.67) Moderate: 2.98 (2.37, 3.75) *Adjusted for low birth weight, urinary fluoride (mg/L)* Overall: 1.41 (1.34, 1.48) Very Mild: 1.64 (1.45 1.86) Mild: 1.57 (1.47, 1.67) Moderate: 2.57 (2.14, 3.08) *Adjusted for urinary creatinine, urinary fluoride (mg/L)* Overall: 1.42 (1.35, 1.50) Very Mild: 1.63 (1.43, 1.86) Mild: 1.59 (1.48, 1.71) Moderate: 2.76 (2.19, 3.48) *Adjusted for age, urine creatinine, sex, BMI, parental education, family income and*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			low birth weight, urinary fluoride (mg/L) Overall: 1.42 (1.35, 1.50) Very Mild: 1.67 (1.48, 1.88) Mild: 1.59 (1.48, 1.72) Moderate: 3.20 (2.49, 4.13)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected according to the same criteria and from the same eligible population. Time frame was not reported in the study.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, the study was adjusted for major confounders (age, sex, BMI, low birth weight, parental education, family income and low birth weight). Urinary fluoride was additionally adjusted for urinary creatinine.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, the study reported on the reasons for exclusion of study participants (history of chronic medical conditions such as kidney, liver, or endocrine disorders, children living in areas where iodine deficiency disorders were endemic, or where exposure to other potential pollutants such as lead, arsenic, or mercury was known/reported).
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride levels in water and urine were assessed suing Ion-selective potentiometry (PF-202-CF; INESA Scientific Instrument Co., Ltd., China)
	Can we be confident in the outcome assessment?	++	Yes, the outcome (DF) was assessed by two experienced dentists who were blinded to children's exposure status, using DFI.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Ahmad 2022 [8]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Pakistan **Participants:** Students (9 – 11 years of age) of madrassa (Islamic religious school) in urban and rural locations within the province of Sindh	**Exposures:** Fluoride levels in • Drinking water • Urine **Method of exposure assessment:** NR **Exposure level:** Mean fluoride levels in urban madrassas (Karachi Central) • Drinking water: 2.04 mg/L • Urine: 5.99 (±3.57) mg/L	**Outcome(s):** • IQ **Method of outcome ascertainment:** • The Raven's Progressive Matrices Intelligence Test • A teacher trained by a psychologist administered the test	**Statistical analysis:** • T-test and Mann-Whitney test were used • Statistical significance at p <0.05 **Results:** N (%) of IQ scores by high (urban) and low (rural) fluoride areas IQ <70 retarded (low) • High fluoride: 2 (3.33) • Low fluoride: 5 (8.33) IQ 70 – 79 borderline (below average) • High fluoride: 4 (6.67) • Low fluoride: 6 (10) IQ 80 – 89 dull normal (low average) • High fluoride: 10 (16.67) • Low fluoride: 9 (15)	• "The significantly higher IQ, 99.95±15.50, of boys in the urban area madrassas with a high drinking water fluoride level compared to the IQ, 92.30±14.97, of boys in the rural area madrassas with a low drinking water fluoride level contradicts the previous reports of higher fluoride levels being associated with a lower IQ. However, several confounding factors were not controlled for in the present study, including the level of parental

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: NR **Sample size:** 120 **Sex N (%):** Girls: 34 (28.3%) **Exclusions:** NR **Source of funding / support:** NR	<u>Mean fluoride levels in rural madrassas (Umerkot)</u> • Drinking water: 1.07 mg/L • Urine: 3.53 (±1.09 mg/L)		<u>IQ 90 – 109 normal (average)</u> • High fluoride: 20 (33.33) • Low fluoride: 19 (31.67) <u>IQ 110 – 119 bright normal (high average)</u> • High fluoride: 16 (26.67) • Low fluoride: 15 (25) <u>IQ 120 – 129 superior (good)</u> • High fluoride: 7 (11.67) • Low fluoride: 6 (10) <u>IQ >129 very superior (excellent)</u> • High fluoride: 1 (1.66) • Low fluoride: 0 (0.0) “No significant difference was present between the IQ distribution in the high and low fluoride areas on chi-square testing after	education, socio-economic status, and the levels of arsenic, lead, and iodine.” (p. 57)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: NR			combining the groups IQ <70 and IQ 70–79, and the groups IQ 120–129 and IQ >129, so that the cells had an n of 5 or more" (p. 56) IQ scores by high (urban) and low (rural) fluoride areas stratified by gender <u>Boys</u> • High fluoride: 99.95 (± 15.50) • Low fluoride: 92.30 (± 14.97) <u>Girls</u> • High fluoride: 96.90 (± 16.31) • Low fluoride: 90.30 (± 15.49)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			“comparing IQ of high fluoride boys and low fluoride boys p<0.05” (p. 57)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	–	NR (eligibility criteria and recruitment time frame not reported)
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	t-test and Mann Whitney tests were used. "several confounding factors were not controlled for including the level of parental education, socio-economic status, and the levels of arsenic, lead, and iodine." (p. 49)
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	Reasons for exclusion NR. "There were more than 230 students registered in madrassa in rural and urban areas and the participants in this cross-sectional study comprised 120 madrassa students, aged 9–11-years-old, in the rural and urban areas of Sindh province, Pakistan. According to the fluoride concentration in the groundwater, the participants were determined using a stratified cluster selection of areas based on the geological survey report of the Government of Pakistan." (p. 54- 55)
Detection	Can we be confident in the exposure characterization?	–	Exposure assessment methods NR
	Can we be confident in the outcome assessment?	–	"The Raven's Progressive Matrices Intelligence Test, with a series of conceptual judgment multiple choice questions in the Urdu and English languages, was employed in the study" (p. 55). Unclear blinding
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Feng 2022 [9]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** Children aged 8-12 years **Sampling time frame:** April-May 2017 **Sample size:** 683	**Exposures:** Fluoride level(s) in: • Urine **Method of exposure assessment:** • Fluoride ion-selective electrode (Shanghai Exactitude Instruments, Shanghai, China) • Creatinine-adjusted urinary fluoride (UFcr) levels were calculated	**Outcome(s):** • Intelligence quotient (IQ).	**Statistical analysis:** • Descriptive analysis • Generalized linear model (GLM) • Multinomial logistic regression **Results:** Mean IQ scores • HFG: 122.61±11.61 • CG: 121.50±12.14 • P=0.290 • Total: 122.05±11.88 Distribution by intelligence level in HFG and CG • Normal: (IQ 90-109): 15.25% (HFG); 17.54% (CG)	• "Excessive fluoride exposure may have adverse effects on children's intelligence, and changes in children's intelligence may be associated with the interaction between fluoride and MTHFD1 polymorphisms." • Note: significant trends in IQ with increasing creatinine-adjusted urinary fluoride were found only in high fluoride group; no significant trends were seen in the total population.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: N (%): Boys: 324 (47.44%) **Exclusions:** • Non-residents • On calcium supplements • Had disorders of calcium or phosphorus metabolism, digestive diseases, or thyroid diseases. • Children with IQ<90 **Source of funding / support:** • The National Natural Science Foundation of China (Nos. 81972981, 82003401, and 81673116) • Key Projects of Colleges and Universities of Henan Education	**Exposure level(s):** Median UFcr (mg/L): 1.33 Children were divided into two groups, high fluoride group (HFG, UFcr>1.33 mg/L) and control group (CG, UFcr≤1.33 mg/L). Mean urinary fluoride [UF, unadjusted for creatinine] (mg/L): • HFG:1.56±0.82 • CG: 0.98±0.62 • P<0.001 • Total: 1.27±0.79 Mean UFcr (mg/L) • HFG: 2.15±0.91 • CG: 0.83±0.30 • P<0.001 • Total: 1.49±0.95	**Method of outcome ascertainment:** • The second revision of the Combined Raven's Test – the Rural in China (CRTRC2) • Children completed the test "independently with the supervision of trained investigators".	• High-normal (IQ 110-119): 25.81% (HFG); 24.85% (CG) • Superior (IQ 120-129): 30.21% (HFG); 33.04% (CG) • Excellent (IQ≥130): 28.74% (HFG); 24.56% (CG) • P=0.539 High fluoride group (HFG) • Change in IQ score per 1.0 mg/L increase in UFcr level: β=-2.502 (95% CI: -4.411, -0.593); p=0.010 • Change in the probability of "excellent" intelligence (IQ≥130) per 1.0 mg/L increase in UFcr level: OR=0.537 (95% CI: 0.290, 0.994); p=0.048 • No significant trend in IQ scores by tertile of UFcr (≤1.63, 1.64-2.14, >2.14 mg/L); p=0.116 Control group	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Department (21A330006) **Author declaration of interest:** no COI			• No significant change in IQ score per 1.0 mg/L increase in UFcr level: p=0.181 • •No significant change in the probability of “excellent” intelligence (IQ≥130) per 1.0 mg/L increase in UFcr level: p=0.659 • No significant trend in IQ scores by tertile of UFcr (≤0.66, 0.67-1.02, >1.02 mg/L); p=0.343 Total • No significant change in IQ score per 1.0 mg/L increase in UFcr level: p=0.376 • No significant change in the probability of “excellent” intelligence (IQ≥130) per 1.0 mg/L increase in UFcr level: p=0.396 • No significant trend in IQ scores by tertile of UFcr (≤1.02, 1.03-1.63, >1.63 mg/L); p=0.426	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Statistically significant gene-environmental interaction on the IQ scores *[Polymorphisms in 4 loci of MTHFD1 related to neurodevelopment (rs11627387, rs1076991, rs2236224, and rs2236225) were analyzed]* • UFcr x rs11627387 x rs1076991 x rs2236224: F=1.669; p=0.021 • UFcr x rs11627387 x rs1076991 x rs2236225: F=1.764; p=0.012 • UFcr x rs11627387 x rs1076991 x rs2236224 x rs2236225: F=1.614; p=0.012	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	All participants were recruited from the same four primary schools at the same time and using the same eligibility criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it was adjusted for major confounders such as children's age, sex, BMI, age at which pregnancy occurred, gestational weeks, birth weight, birth modes, and paternal and maternal education level.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, the study reported on the reasons for exclusion of study participants (non-residents, on calcium

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			supplements, had disorders of calcium or phosphorus metabolism, digestive diseases, or thyroid diseases, and children with IQ<90).
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in urine using fluoride ion-selective electrode (Shanghai Exactitude Instruments, Shanghai, China). Creatinine-adjusted urinary fluoride levels were calculated to correct for urine dilution.
	Can we be confident in the outcome assessment?	–	The Combined Raven's Test – the Rural in China (CRTRC2) was completed by children under supervision of "trained investigators". It is not reported whether the children and/or the "trained investigators" were aware of the exposure status.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcome (children intelligence, IQ) discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were	++	None identified

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
	appropriate and researchers adhered to the study protocol)?	

García-Escobar 2022 [10]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** India **Participants:** 785 subjects aged 10-60 years **Sampling time frame:** NR	**Exposures** Fluoride levels in • Drinking water **Method of exposure assessment:** • Fluoride levels in water: “ion	**Outcome(s):** Dental fluorosis	**Statistical analysis:** • Fisher’s exact test • Spearman’s rank order correlation • Method for estimation of ORs not reported. **Results:** Overall prevalence • 94.6% (DI) • 94.4 (TFI)	• “Patients from rural communities of the Anantapur district showed a high prevalence (over 90%) of dental fluorosis. Moreover, the Anantapur population presents a high number of moderate and severe cases (over 60%), while other populations

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size: 785 **Sex: N (%):** Men: 322 (41.3%) **Exclusions:** • Orofacial malformations or pathologies that could make examination difficult • Systemic pathology affecting fluoride metabolism • Absence of permanent or definitive teeth • Dental surface wear or stains due to tobacco, betel, or another chewing habit	chromatography according to the parameters for potable waters for public consumption in Spain (R.D. 140/2003)" **Exposure level(s):** • Water fluoride (ppm): 1.1 to 2.92 (mean 1.71, median 1.5)	**Method of outcome ascertainment:** • The Dean Index (DI) • The Thylstrup and Fejerskov Index (TFI)	<u>Prevalence of Moderate–Severe (MS) cases (DI) and TFI score 4–9 cases</u> [DI MS group corresponds to TFI 4–9] • 62.8% (DI MS) • 73.1% (TFI 4-9) <u>Prevalence of fluorosis among those consuming water with water fluoride ≤1.5 ppm</u> • 54.3% (DI) • 54.5% (TFI) <u>Prevalence of DI MS and TFI 4-9 among those consuming water with water fluoride ≤1.5 ppm</u> • 33.2% (DI MS) • 39.9% (TFI 4-9) <u>OR (95% CI)</u>	showed less severe forms of fluorosis, despite reporting superior fluoride levels to those found in the Anantapur drinking water." • "The severity of fluorosis concerning fluoride concentration levels in drinking water in Anantapur suggests that other factors are involved in the severity of the dental fluorosis observed. A potential change in the biological susceptibility of the population to the toxin, due to the long-term

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Excessive bacterial dental plaque or calculus • Patients requiring urgent dental attention • Patients with missing data • Patients whose parents or grandparents came from a community outside Anantapur. **Source of funding / support:** No external funding **Author declaration of interest:** No COI			DI MS • ≤1.5 ppm: reference • >1.5 ppm: 1.81 (1.34–2.45) • P=0.000 TFI 4-9 • ≤1.5 ppm: reference • >1.5 ppm: 1.79 (1.28–2.5) • P=0.000 Spearman's rank order correlation between water fluoride and moderate-severe fluorosis • DI MS: R_s=0.527; p=0.064 • TFI 4-9: R_s=0.610; p=0.027	exposition (including several generations) could explain the phenomenon…"

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	NA Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants selected using same criteria. Sampling time frame not reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	NA	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in water using ion chromatography
	Can we be confident in the outcome assessment?	++	DF examined using the Thysltrup and Fejerskov criteria and Dean Index
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Goodman 2022 [11]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cohort (ELEMENT) **Country:** Mexico	**Exposures:** Fluoride level in • Maternal urine collected during one or more trimesters of pregnancy	**Outcome(s):** • Children's IQ	**Statistical analysis:** • Generalized estimating equation (GEE) population averaged models for panel data with an autoregressive correlation structure (estimation across time). • Age-stratified multiple linear regression analyses (estimation at each time point)	• "… prenatal exposure to fluoride is associated with sustained impacts on IQ." • "… an increment of 0.5 mg/L in maternal urinary fluoride concentration was associated with a 2-

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: • Women who were planning to conceive or were pregnant at <14 weeks gestation (Cohorts 2A and Cohort 3 of the ELEMENT project). • Children examined at ages 4, 5, and 6–12 years **Sampling time frame:** Recruitment: Cohort 2A in 1997-1999; Cohort 3 in 2001-2003 **Sample size:**	**Method of exposure assessment:** • A modification of the hexamethyldisiloxane (Sigma Chemical Co., USA) microdiffusion method with the ion-selective electrode • An average of all available maternal urinary fluoride adjusted for creatinine concentrations during pregnancy (1 to 3 samples) was used as the exposure measure.		**Results:** Changes in cognitive sore per 0.5 mg/L increase in MUFcre <u>GEE population-averaged models</u> • FSIQ/GCI: B=-2.12 (95% CI: -3.49, -0.75); p=0.002 • PIQ: B=-2.63 (95% CI: -3.87, -1.40); p<0.001 • VIQ: B=-1.29 (95% CI: -2.60, 0.01); p=0.053 • No interactions were between MUFcre and time (p>0.10). • No interaction between MUFcre and child sex (p>0.10) <u>Linear regression analysis</u> Age 4 • GCI: B=-2.12 (95% CI: -3.83, -0.41); p=0.015 • PIQ: B=-3.08 (95% CI: -4.69, -1.47); p<0.001)	point decrement in children's Full-Scale IQ scores". • "Non-verbal abilities may be more susceptible to impairment from prenatal fluoride exposure as compared to verbal abilities." • "These results were found among mother-child pairs living in a region of Mexico in which fluoride is added to salt."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Primary sample with complete covariate, maternal urinary fluoride, and outcome data for at least two time points: 348 mother-child dyads • Examined at age 4 years: 386 • Examined at age 5: 308 • Examined at age 6-12: 278 **Sex: N (%):** Boys: • Primary sample: 167 (47.99%) • Age 4: 183 (47.41%) • Age 5: 151 (49.03%)	**Exposure level(s):** • Creatinine-adjusted maternal urinary fluoride (MUFcre, µg/L): 0.14 to 3.01; mean 0.90 (SD 0.39), median 0.83; IQR 0.64-1.11	**Method of outcome ascertainment:** McCarthy Scales of Children's Abilities (MSCA) translated into Spanish to children aged 4 and 5 years • Verbal scale (VIQ, a measure of verbal	• VIQ: B=-0.81 (95% CI: -2.30, 0.69); p>0.05 Age 5 • GCI: B=-1.97 (95% CI: -3.64, -0.30); p=0.021 • PIQ: B=-2.46 (95% CI: 4.04, -0.87); p=0.003 • VIQ: B=-1.24 (95% CI: -2.97, 0.49); p>0.05 Age 6-12 • FSIQ: B=-2.01 (95% CI: -3.66, -0.46); p=0.012 • PIQ: B=-1.80 (95% CI: -3.39, -0.21); p=0.027 • VIQ: B=-1.93 (95% CI: -3.67, -0.18); p=0.031 • No interaction between MUFcre and child sex <u>Sensitivity analyses (GEE models), B (95% CI)</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Age 6-12: 132 (47.48%) **Exclusions:** Women with a history of psychiatric disorders, substance use, high-risk pregnancy, or		reasoning and comprehension) • Perceptual-performance scale (PIQ, a measure of nonverbal reasoning and perceptual information processing) • General Cognitive Index (GCI), the standardized composite score Spanish version of Wechsler Abbreviated	FSIQ/GCI. • Model A[v]: -2.10 (-3.47, -0.73) • Model A + number/timing of urine samples[vi]: -2.12 (-3.49, -0.75) • Model A – IQ score<70[vii]: -1.67 (-2.93, -0.41) • Model A – Cohort 3 Ca[viii]: -1.98 (-3.70, -0.27) • Model A – Maternal IQ[ix]: -2.40 (-3.79, -1.01) • Model A + Maternal IQ[x]: -2.09 (-3.44, -0.73)	

[v] GEE models adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, time of testing, smoking history (ever smoked during the pregnancy vs. non-smoker), marital status (married vs. others), maternal age at delivery, maternal education, and cohort/calcium treatment.

[vi] Number/timing of urine samples included as a covariate

[vii] Excluding cases with FSIQ/GCI, PIQ, or VIQ scores less than 70

[viii] Subset of cases who received calcium supplementation

[ix] Subset of cases who have data on maternal IQ

[x] Subset of cases who have data on maternal IQ, adjusted for maternal IQ

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
other medical conditions **Source of funding / support:** • The American British Cowdray Hospital provided facilities for the ELEMENT research. • U.S. National Institutes of Health (NIH;		Scale of Intelligence (WASI) to children aged 6-12 years. • Verbal IQ (VIQ, a measure of verbal reasoning and comprehension) • Performance (PIQ, a measure of nonverbal reasoning and spatial processing) • Full-Scale intelligence (FSIQ, a measure of global intellectual functioning)	• Model A – HOME[xi]: -2.33 (-4.46, -0.20) • Model A + HOME[xii]: -2.11 (-4.06, -0.16) • Model A – Patella Lead[xiii]: -2.42 (-3.98, -0.86) • Model A + Patella Lead[xiv]: -2.41 (-3.98, -0.85) • Model A – Tibia Lead[xv]: -2.75 (-4.61, -0.89) • Model A + Tibia Lead[xvi]: -2.23 (-4.09, - 0.38) • Model A – Tibia and Patella Lead[xvii]: -2.73 (-4.71, -0.76) • Model A + Tibia and Patella Lead[xviii]: -2.20 (-4.18, -0.22)	

[xi] Subset of cases who have data on Home Observation for the Measurement of the Environment (HOME) scores

[xii] Subset of cases with HOME score, adjusted for HOME score

[xiii] Subset of cases who have data on maternal patella lead

[xiv] Subset of cases with data on maternal patella lead, adjusted for maternal patella lead

[xv] Subset of cases who have data on maternal tibia lead

[xvi] Subset of cases with data on maternal tibia lead, adjusted for maternal tibia lead

[xvii] Subset of cases who have data on maternal tibia and patella lead

[xviii] Subset of cases with data on maternal tibia and patella lead, adjusted for maternal tibia and patella lead

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
grants R01ES021446 and R01-ES007821) • The National Institute of Environmental Health Sciences/the U.S. Environmental Protection Agency (NIEHS/EPA; grant P01ES022844, 83543601) • The NIEHS (grant P42-ES05947, P20ES018171) • NIEHS Center Grant P30ES017885) • National Institute of Public Health/Ministry		Each child was evaluated by one of three psychologists supervised by experienced developmental psychologist. The inter-examiner reliability: r>0.90 (MSCA); not assessed for WASI	PIQ • Model A: 2.61 (-3.85, -1.38) • Model A + number/timing of urine samples: -2.63 (-3.86, -1.39) • Model A – IQ score<70: -2.61 (-3.81, -1.42) • Model A – Cohort 3 Ca: -3.13 (-4.67, -1.58) • Model A – Maternal IQ: -2.78 (4.04, -1.52) • Model A + Maternal IQ: -2.46 (-3.68, -1.24) • Model A – HOME: -3.67 (-5.52, -1.82) • Model A + HOME: -3.44 (-5.15, -1.72) • Model A – Patella Lead: -2.66 (-4.05, -1.27) • Model A + Patella Lead: -2.65 (-4.04, -1.27) • Model A – Tibia Lead: -2.81 (-4.46, -1.16) • Model A + Tibia Lead: -2.41 (-4.07, -0.76)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
of Health of Mexico **Author declaration of interest:** No COI			• Model A – Tibia and Patella Lead: -2.75 (-4.50, -1.00) • Model A + Tibia and Patella Lead: -2.32 (-4.08, -0.56) VIQ • Model A: -1.28 (-2.58, 0.03) • Model A + number/timing of urine samples: -1.30 (-2.60, 0.01) • Model A – IQ score<70: -1.05 (-2.31, 0.21) • Model A – Cohort 3 Ca: -0.69 (-2.31, 0.94) • Model A – Maternal IQ: -1.55 (-2.86, -0.24) • Model A + Maternal IQ: -1.33 (-2.62, -0.04) • Model A – HOME: -0.71 (-2.72, 1.30) • Model A + HOME: -0.54 (-2.43, 1.35) • Model A – Patella Lead: -1.62 (-3.12, -0.11) • Model A + Patella Lead: -1.62 (-3.13, -0.11)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Model A – Tibia Lead: -2.09 (-3.88, -0.31) • Model A + Tibia Lead: -1.65 (-3.44, 0.14) • Model A – Tibia and Patella Lead: -2.09 (-3.99, -0.19) • Model A + Tibia and Patella Lead: -1.63 (-3.55, 0.28)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Mother-child pairs were enrolled from three hospitals in Mexico City serving low to middle income families. Eligibility criteria were slightly different between the two cohorts (2A and 3), but there is no indication that they differed in relation to

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			fluoride exposure level. Time frame was different for the two cohorts (2A and 3). More information about study participants can be found in Perng et al. 2019[xix].
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it was adjusted for major confounders such as maternal education, maternal age at delivery, marital status at delivery, maternal smoking, gestational age, weight at birth, birth order, child age at each outcome measurement, and cohort.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, the study reported on the reasons for exclusion of study participants (women with a history of psychiatric disorders, substance use, high-risk

[xix] https://bmjopen.bmj.com/content/9/8/e030427

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			pregnancy, or other medical conditions). Although it is not reported, there is no indication that losses to follow-up were related to intelligence level.
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in maternal urine using a modification of the hexamethyldisiloxane (Sigma Chemical Co., USA) microdiffusion method with the ion-selective electrode
	Can we be confident in the outcome assessment?	++	Yes, IQ was consistently assessed by one of three psychologists who was unaware to the child's prenatal fluoride exposure and supervised by an experienced developmental psychologist. The age-appropriate assessment tools included the McCarthy Scales of Children's Abilities, MSCA, translated into Spanish (administered at ages 4 and 5 years), and the Spanish version of Wechsler Abbreviated Scale of Intelligence, WASI (administered at age 6-12 years).

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcome (children intelligence, IQ) discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Gupta 2022 [12]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Case-Control Study	**Exposures:** <u>Fluoride levels in:</u> • Drinking water • Serum	**Outcome(s):** • Dental fluorosis • Skeletal fluorosis	**Statistical analysis:** • Descriptive analysis • Analysis of variance	• "Besides high concentrations of fluoride in potable water, poor socio-economic status

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: India **Participants:** Subjects: from endemic villages, controls: from non-endemic villages **Sampling time frame:** 2014-2015 **Sample size:** 180 **Sex: N (%):** NR **Exclusions:** Neonates, children, pregnant women and patients with other severe & chronic diseases	**Method of exposure assessment:** • Drinking water: Thermo scientific orion 9609 BNWP ion selective fluoride electrode • Serum: Semi auto analyzer (Model CHEM 400), Electronics India. **Exposure level(s):** • Mean drinking water fluoride levels 1.16-7.56 ppm	**Method of outcome ascertainment:** • Dental Fluorosis: NR • Skeletal Fluorosis: NR	**Results:** Water fluoride concentration associated with: • Dental fluorosis: 0.67-0.83 ppm • Skeletal fluorosis: 0.43-0.83 ppm	and nutritional deficiency also contribute to fluorosis in exposed individuals from endemic regions." • For the individuals residing in an endemic area and consuming the same high fluoride containing drinking water which doesn't have visible symptoms of dental or skeletal fluorosis, individuals might be considered in a preclinical stage of fluorosis and may develop symptoms of fluorosis in subsequent years. The finding of this study might be a

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: • UGC, New Delhi • Chhattisgarh Council of Science and Technology **Author declaration of interest:** No COI				preliminary screening for those individuals. However, urine and blood fluoride analyses of the subjects are also needed for further confirmation.”

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe, according to the same criteria and from the same eligible population.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment					
Bias domain	***Criterion***	***Response***			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable		
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (Neonates, children, pregnant women and patients with other severe & chronic diseases)		
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels Drinking water samples from the study areas were collected and estimated for the fluoride content with the help of Thermo-scientific Orion 9609 BNWP ion selective fluoride electrode. Fluoride concentrations in serum was measured by the Semi auto analyzer (Model CHEM 400), Electronics India.		
	Can we be confident in the outcome assessment?	–	NR	–	NR
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Ibarluzea 2022 [13]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cohort **Country:** Spain	**Routes of exposures:** Fluoride level in • Maternal urine collected in the first and third trimesters of pregnancy	**Outcome(s):** • Children's cognition/intelligence	**Statistical analysis**[xx]**:** • Student's t tests • One-way analysis of variance • Pearson correlations • Multiple linear regression	• "We observed no negative effects on children's cognition and even found positive associations for verbal, performance, numeric, memory scores and GCI, in boys at the age of 4 years, although when Hg levels were included in the model only verbal and GCI at week 32 and whole pregnancy remained significant or marginally significant."
Participants: Pregnant women Children examined at ages 1 and 4 years **Sampling time frame:** Recruitment of pregnant women between 1997 and 2008 in different study	**Method of exposure assessment:** • Potentiometry using an ion-selective electrode (DX219-F, Mettler Toledo) • Urinary fluoride levels were		**Results:** **Changes in cognitive score per unit (mg/g) increase in maternal creatinine-adjusted urinary fluoride (MUFcr), β (95% CI)**[xxi] Bayley Mental Development Index (MDI)	

[xx] Student's t-test, one-way ANOVA and Pearson correlation were used to select variables for multiple linear regression (with p<0.2)

[xxi] Adjusted for child's age at testing (only for McCarthy), order of the child (between siblings), nursery at 14 months, breastfeeding, maternal social class, IQ and smoking

areas (Guxen et al. 2012)[xxii] **Sample size:** • Assessed at age 1 year: 316 mother-child pairs • Assessed at ages 1 and 4 years: 248 mother-child pairs	adjusted for creatinine			
Sex: N (%): Boys: • Assessed at age 1 year: 146 (46.2%) • Assessed at age 4 years: 125 (50.4%)	**Exposure level(s):** **Fluoride levels in drinking water** • Community fluoridated drinking water systems: mean 0.81 (SD 0.15) mg/L • Community non-fluoridated drinking water systems: <0.1 mg/L **Mean (95% CI)**	**Method of outcome ascertainment:** • Bayley Scales of Infant Development (BSID) at age 1 year • McCarthy Scales of Children's Abilities (MSCA)[xxiv]	***Both trimesters MUFcr*** • All: 1.48 (-4.2, 7.16) • Boys: 3.84 (-5.04, 12.72) • Girls: 0.75 (-6.92, 8.43) ***Week 12 MUFcr*** • All: 0.55 (- 4.64, 5.74) • Boys: 2.96 (-5.09, 11.01) • Girls: -1 (-8.07, 6.07) ***Week 32 MUFcr*** • All: 1.52 (-2.92, 5.97) • Boys: 2.50 (-4.46, 9.46) • Girls: 1.7 (-4.30, 7.71) McCarthy, verbal ***Both trimesters MUFcr*** • All: 13.86 (3.91, 23.82) • Boys: 13.38 (2.81, 23.95) • Girls: -1.31 (-9.35, 6.74) • P<0.05 ***Week 12 MUFcr*** • All: 1.11 (-4.86, 7.07) • Boys: 3.78 (-6.16, 13.71) • Girls: -0.91 (-8.78, 6.96) ***Week 32 MUFcr***	• "The positive associations between MUFcr and cognitive functions seemed to be more evident in children of mothers who lived their pregnancy in the nonfluoridated zones." • "The associations have been seen with MUFcr of the third trimester and not with those of the first one." • "As there is not information of MUFcr of the second trimester of pregnancy, it is difficult to identify a window of exposure related to the effect, but the lack of
Exclusions: At recruitment • Maternal age <16 years • Multiple pregnancy • Pregnancy achieved with assisted reproduction techniques	**maternal**			

[xxii] Guxens M, Ballester F, Espada M, Fernández MF, Grimalt JO, Ibarluzea J, Olea N, Rebagliato M, Tardón A, Torrent M, Vioque J, Vrijheid M, Sunyer J; INMA Project. Cohort Profile: the INMA--INfancia y Medio Ambiente--(Environment and Childhood) Project. Int J Epidemiol. 2012 Aug;41(4):930-40. doi: 10.1093/ije/dyr054. Epub 2011 Apr 5. PMID: 21471022

[xxiv] The motor scale of the MSCA was not included in this study.

• Not planning birth in the referral hospital • Communication problems in Spanish or Basque Analytical sample • Incomplete data [To be included, participants had to have 1) data on neuropsychological assessment at 1 year of age; 2) data on neuropsychological assessment at 4 years of age provided they also had assessment data at 1 year; 3) maternal urinary creatinine adjusted fluoride levels at the first and third trimesters of pregnancy.]	**creatinine-adjusted urinary fluoride levels (mg/g creatinine)**[xxiii] Assessed at age 1 year • Both trimesters: 0.66 (0.61; 0.70) • Week 12 of pregnancy: 0.57 (0.52; 0.62) • Week 32 of pregnancy: 0.74 (0.69; 0.79) • P<0.001 [1st vs. 3rd trimester] Assessed at age 4 years • Both trimesters: 0.64 (0.59; 0.68)	• All: 12.01 (4.82, 19.19) • Boys: 11.79 (4.22, 19.36) • Girls: -0.93 (-7.01, 5.15) • P<0.01 McCarthy, performance ***Both trimesters MUFcr*** • All: 5.86 (0.32, 11.39) • Boys: 12.24 (2.87, 21.61) • Girls: 2.03 (-4.77, 8.83) • P<0.05 ***Week 12 MUFcr*** • All: 4.63 (-0.57, 9.82) • Boys: 9.11 (0.47, 17.75) • Girls: 1.10 (-5.53, 7.73) ***Week 32 MUFcr*** • All: 3.68 (-0.49, 7.85) • Boys: 7.17 (0.24, 14.09) • Girls: 1.69 (-3.44, 6.83) • P<0.05 McCarthy, numeric ***Both trimesters MUFcr*** • All: 6.22 (0.65, 11.79 • Boys: 11.09 (1.79, 20.4)	associations in the first trimester indicate that the effects are associated with later periods in pregnancy." • "A positive association between MUF and GCI scores and other measures of cognitive functions at 4 years of age is observed among boys in a prospective birth cohort in Spain. The current findings contradict, with a few exceptions, results obtained previously in cross-sectional and prospective studies."
Source of funding / support[xxv]**:**			

[xxiii] Detailed data on maternal creatinine-adjusted urinary fluoride levels by maternal and children's characteristics are reported in Supplementary tables S2, S3 and S5

[xxv] Information from Guxen et al. 2012.

• The Instituto de Salud Carlos III, Red de Centros de investigación en Epidemiología y Salud Pública (RCESP) • CIBER Epidemiología y Salud Pública (CIBERESP) • The Fondo de Investigación Sanitaria • The European Union's 6th and 7th Framework Programmes (Hiwate, Escape, Hitea and Contamed projects) • The Ministerio de Educación y Ciencia, the Generalitat de Catalunya • The Centre for Research in Environmental Epidemiology (CREAL) of Barcelona	• Week 12 of pregnancy: 0.55 (0.50;0.60) • Week 32 of pregnancy: 0.73 (0.67;0.79) • P<0.001 [1st vs. 3rd trimester] **Whole pregnancy mean (SD) maternal urinary fluoride (mg/L)** <u>Assessed at age 1 year</u> • Non-fluoridated zone: 0.36 (0.21) • Fluoridated zone: 0.65 (0.29) • P<0.001 <u>Assessed at age 4 years</u> • Non-fluoridated zone: 0.35 (0.20) • Fluoridated zone: 0.62 (0.26) • P<0.001	• Girls: 3.03 (-3.96, 10.03) • P<0.05 ***Week 12 MUFcr*** • All: 4.47 (-0.79, 9.73) • Boys: 5.03 (-3.65, 13.7) • Girls: 2.92 (-3.95, 9.78) ***Week 32 MUFcr*** • All: 4.13 (-0.07, 8.32) • Boys: 8.56 (1.81, 15.31) • Girls: 1.55 (-3.74, 6.85) • P<0.05 <u>McCarthy, memory</u> ***Both trimesters MUFcr*** • All: 11.63 (2.62, 20.63) • Boys: 11.3 (1.90, 20.7) • Girls: -2.12 (-9.32, 5.09) • P<0.05 ***Week 12 MUFcr*** • All: 1.71 (-3.66, 7.09) • Boys: 4.28 (-4.51, 13.06) • Girls: -1.40 (-8.46, 5.67) ***Week 32 MUFcr*** • All: 9.2 (2.67, 15.73) • Boys: 9.26 (2.47, 16.05) • Girls: -1.72 (-7.17, 3.72) • P<0.01

• The Fundació La Caixa, the Fundació Roger Torné • The Consejería de Salud de Andalucía • The Junta the Andalucía • The Conselleria de Sanitat de la Generalitat Valenciana • The CAJASTUR—Caja Asturias • The Spanish Association against the Cancer (AECC) (Delegación Provincial Asturias) • The Departamento de Sanidad-Gobierno Vasco • The Diputación Floral de Gipuzkoa • The University of Oviedo, the KUTXA – Caja Gipuzkoa San Sebastián • The city councils of Zumarraga, Urretxu, Legazpi, Azpeitia, Beasain and Azkoitia in Gipuzkoa	**Both trimesters mean (SD) creatinine-adjusted maternal urinary fluoride (mg/g creatinine)** <u>Assessed at age 1 year</u> • Non-fluoridated zone: 0.46 (0.25) • Fluoridated zone: 0.84 (0.40) • P<0.001 <u>Assessed at age 4 years</u> • Non-fluoridated zone: 0.45 (0.26) • Fluoridated zone: 0.82 (0.39) • P<0.001	<u>McCarthy, general cognitive</u> ***Both trimesters MUFcr*** • All: 15.4 (6.32, 24.48) • Boys: 15.03 (5.3, 24.75) • Girls: -0.02 (-7.16, 7.12) • P<0.01 ***Week 12 MUFcr*** • All: 3.37 (-2.09, 8.83) • Boys: 7.14 (-2.06, 16.33) • Girls: 0.21 (-6.77, 7.19) ***Week 32 MUFcr*** • All: 11.48 (4.88, 18.08) • Boys: 11.39 (4.33, 18.44) • Girls: -0.16 (-5.55, 5.23) • P<0.01 **Changes in cognitive score per unit (mg/g) increase in MUFcr, β (95% CI) <u>additionally adjusted for cord blood Hg levels</u>.** <u>Bayley Mental Development Index (MDI)</u> ***Both trimesters MUFcr*** • All: 2.67 (-3.46, 8.81)

Author declaration of **interest:** no COI •	• No significant interaction by sex ***Week 12 MUFcr*** • All: 0.89 (-4.55, 6.32) • No significant interaction by sex ***Week 32 MUFcr*** • All: 2.65 (-2.14, 7.45) • No significant interaction by sex <u>McCarthy, verbal</u> ***Both trimesters MUFcr*** • All: 9.4 (-1.78, 20.57) • Boys: -- • Girls: -2.07 (-10, 5.87) • P<0.1 ***Week 12 MUFcr*** • All: -1.5 (-7.53, 4.54) • No significant interaction by sex ***Week 32 MUFcr*** • All: 9.74 (1.75, 17.74) • Boys: -- • Girls: -0.74 (-6.72, 5.25) • P<0.05 <u>McCarthy, performance</u> ***Both trimesters MUFcr*** • All: 4.41 (-1.59, 10.41)

	• No significant interaction by sex ***Week 12 MUFcr*** • All: 3.85 (-1.62, 9.33) • No significant interaction by sex ***Week 32 MUFcr*** • All: 2.33 (-2.15, 6.82) • No significant interaction by sex <u>McCarthy, numeric</u> ***Both trimesters MUFcr*** • All: 5.28 (-0.54, 11.1) • No significant interaction by sex ***Week 12 MUFcr*** • All: 3.38 (-1.96, 8.71) • No significant interaction by sex ***Week 32 MUFcr*** • All: 3.47 (-0.88, 7.82) • No significant interaction by sex <u>McCarthy, memory</u> ***Both trimesters MUFcr*** • All: 0.8 (-5.3, 6.9) • No significant interaction by sex ***Week 12 MUFcr***

	• All: -0.52 (-6.06, 5.02) • No significant interaction by sex ***Week 32 MUFcr*** • All: 1.15 (-3.4, 5.69) • No significant interaction by sex <u>McCarthy, general cognitive</u> ***Both trimesters MUFcr*** • All: 10.54 (0.19, 20.89) • Boys: -- • Girls: -0.83 (-8.18, 6.52) • P<0.05 ***Week 12 MUFcr*** • All: 1 (-4.61, 6.61) • No significant interaction by sex: ***Week 32 MUFcr*** • All: 8.15 (0.69, 15.61) • Boys: -- • Girls: -0.46 (-6.04, 5.12) • P<0.05
	Changes in cognitive score per unit (mg/g) increase in MUFcr, β (95% CI), <u>stratified by</u>

	<u>fluoridated and non-fluoridated zone</u> <u>Bayley Mental Development Index (MDI)</u> ***Both trimesters MUFcr*** • Both zones/non-fluoridated: -0.52 (-7, 5.95) • No significant interaction by zone ***Week 12 MUFcr*** • Both zones/non-fluoridated: -1 (-6.66, 4.65) • No significant interaction by zone ***Week 32 MUFcr*** • Both zones/non-fluoridated: 0.33 (-4.52, 5.19) • No significant interaction by zone <u>McCarthy, verbal</u> ***Both trimesters MUFcr*** • Both zones/non-fluoridated: 15.58 (3.71, 27.45) • Fluoridated zone: -2.4 (-11.17, 6.37) • P<0.01

Week 12 MUFcr

- Both zones/non-fluoridated: 0.27 (-6.12, 6.65)
- No significant interaction by zone

Week 32 MUFcr

- Both zones/non-fluoridated: 16.11 (7.4, 24.81)
- Fluoridated zone: -2.3 (-8.6 , 3.99)
- P<0.01

<u>McCarthy, performance</u>

Both trimesters MUFcr

- Both zones/non-fluoridated: 7.82 (1.58, 14.07)
- Fluoridated zone: not reported
- P<0.05

Week 12 MUFcr

- Both zones/non-fluoridated: 5.5 (-0.07, 11.07)
- No significant interaction by zone

Week 32 MUFcr

	• Both zones/non-fluoridated: 4.67 (0.08, 9.26) • Fluoridated zone: not reported • P<0.05 <u>McCarthy, numeric</u> ***Both trimesters MUFcr*** • Both zones/non-fluoridated: 4.08 (-2.21, 10.36) • No significant interaction by zone ***Week 12 MUFcr*** • Both zones/non-fluoridated: 2.63 (-2.96, 8.23) • No significant interaction by zone ***Week 32 MUFcr*** • Both zones/non-fluoridated: 2.53 (-2.06, 7.13) • No significant interaction by zone <u>McCarthy, memory</u> ***Both trimesters MUFcr*** • Both zones/non-fluoridated: 2.71 (-3.77 , 9.18)

	• No significant interaction by zone ***Week 12 MUFcr*** • Both zones/non-fluoridated: 1.01 (-4.74, 6.77) • No significant interaction by zone ***Week 32 MUFcr*** • Both zones/non-fluoridated: 2.17 (-2.56, 6.9) • No significant interaction by zone: <u>McCarthy, general cognitive</u> ***Both trimesters MUFcr*** • Both zones/non-fluoridated: 15.46 (4.55, 26.36) • Fluoridated zone: 1.96 (-6.09, 10.02) • P<0.01 ***Week 12 MUFcr*** • Both zones/non-fluoridated: 3.5 (-2.36, 9.36) • No significant interaction by zone ***Week 32 MUFcr***

		• Both zones/non-fluoridated: 12.88 (4.82, 20.94) • Fluoridated zone: 0.11 (-5.73, 5.95) • P<0.01 **Analyses stratified by fluoridated and non-fluoridated zone, <u>boys only</u>** • Significant associations only in non-fluoridated zones [see supplementary table S21 for details.] **Analyses stratified by maternal social class** • "more positive and significant associations were observed in children of mothers with a better social position" [see supplementary table S22] **Analyses stratified by quality of the family context; <u>boys only</u>** • Statistically significant associations only in families with a lower

	quality of the family context (supplementary table S23) **Other analyses** • Inclusion of other variables, such as other neurotoxicants (As, Mn, Pb, As x Pb), iodine, quality child's family context (HES), deprivation index did not substantially change the results. • Analyses including women with only one sample of urine available (first or third trimester), adjustment for zone (fluoridated vs non-fluoridated), or excluding extreme low scores of cognitive functions (less than 2 SD) did not substantially change the results

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable
	Was allocation to study groups adequately concealed?	N/A Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Did selection of study participants result in appropriate comparison groups?	++	Mother-child pairs were enrolled from Gipuzkoa, Spain. Pregnant women were recruited between 1997- 2008. Their children were assessed at the age of 1 and 4 years. More information about study participants can be found in Guxen et al. 2012.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, study accounted for major confounders such as maternal characteristics (sociodemographic, behavioral and reproductive), maternal habits (smoking, type of water consumed) and child characteristics (sex, age, order of the child among siblings, breastfeeding, small for gestational age, and prematurity) and child habits (nursery attendance at 14 months). Adjustments also included creatinine, and Hg in umbilical cord blood, urinary iodine and urinary creatinine and specific gravity.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Mother-child pairs were enrolled from Gipuzkoa, Spain. Pregnant women were recruited between 1997- 2008. Their children were assessed at the age of 1 and 4 years. More information about study participants can be found in Guxen et al. 2012.
Detection	Can we be confident in the exposure characterization?	++	Study reported on source and intake of drinking water (tap or bottled) including food and drink, during the first and third trimesters. Bottled water intake was calculated based on the information provided by the mothers. Maternal urinary

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			fluoride was measured by potentiometry using an ion-selective electrode (DX219-F, Mettler Toledo).
	Can we be confident in the outcome assessment?	++	Yes, children's neuropsychological development was consistently assessed using the Bayley Scales of Infant Development (BSID) (Bayley, 1977) and a standardized version of the McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population (McCarthy, 2009) respectively. Assessments were conducted by specially trained neuropsychologists who were blinded to the child's fluoride's exposure status.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Kaur 2022 [14]

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: • Original study **Study design:** • Cross-sectional **Country:** • India **Participants:** • School children (12-13 years of age) residing in Dhand of Amer Tehsil, Mohanpura, or Muhana of Sanganer Tehsil. **Sampling time frame:**	**Exposures:** <u>Fluoride levels in</u> • Water • Urine **Method of exposure assessment:** • Water fluoride: Acquired from the Public Health Engineering Department • Urine fluoride: Selective Ion Electrode Technique **Exposure level:** <u>Water fluoride concentration by group</u> • Group A: 2 ppm	**Outcome(s):** • IQ **Method of outcome ascertainment:** • Raven's Colored Progressive Matrices intelligence test	**Statistical analysis:** • One-way ANOVA test and paired t-test were used • Statistical significance at $p < 0.05$ **Results:** Correlation between IQ and urinary fluoride level • Group A: r = -0.161, p = > 0.05 • Group B: r = -0.485, p = < 0.01 • Group C: r = -0.334, p = < 0.05	• "No statistically significant correlation (p> 0.05) existed between fluoride excretion and IQ in Group A children. But there was a statistically significant correlation between fluoride excretion and IQ level in Group B (p<0.01) and Group C (p< 0.05). As the level of fluoride ion concentration in urine increased, there was a significant decrease in IQ level" (p. 3) • "The results indicated that there was a

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• September 2011 – October 2011 **Sample size:** • N = 90 **Sex N (%):** • NR **Exclusions:** • Those with history of head trauma or injury • Those with congenital or acquired neurological disorders • Those with psychological disorders **Source of funding / support:**	• Group B: 5 ppm • Group C: 2 – 5 ppm <u>Urinary fluoride concentration by group</u> • Group A: 1.60ppm • Group B: 6.82 ppm • Group C: 2.69 ppm			positive correlation between excess fluoride in drinking water and IQ." (p. 1)

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• None **Author declaration of interest:** • No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants recruited using same eligibility criteria and recruited within same time frame
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	ANOVA test and t-tests were conducted for statistical analysis.
Performance	Were experimental conditions identical across study groups?	NA	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	"The total number of school children aged 12-13 years at Dhand, Mohanpura, and Muhana was 35, 42, and 39, respectively. Children with a history of trauma or injury to the head and those affected by any congenital or acquired neurological disorders or psychological disorders were excluded from the study. Thirty children were randomly allocated from each school into their respective groups. The children were divided into three groups: Group A (Fluoride concentration of 2 ppm), Group B (Fluoride concentration of 5 ppm), and Group C (Fluoride concentration of 2-5 ppm)."
Detection	Can we be confident in the exposure characterization?	++	Water fluoride data was acquired from the Public Health Engineering Department. Urinary fluoride measured using Selective Ion Electrode Technique
	Can we be confident in the outcome assessment?	+	"The IQ of the children was measured using Raven's Coloured Progressive Matrices™ intelligence test [8], which consists of a series of multiple-choice questions. Before administering the test, a friendly explanation of the important instructions was given by a single examiner to avoid mental stress for those taking the test. Children

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			were made to sit in a manner to ensure that they couldn't talk with each other." (p. 2). Unclear blinding.
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Marques 2022 [15]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Brazil **Participants:**	**Exposures** Fluoride levels in • Drinking water	**Outcome(s):** Dental fluorosis	**Statistical analysis:** • Chi-square test • Student's t tests • Logistic regression **Results:**	• "The prevalence of dental fluorosis at all levels was higher in fluoridated areas, however, in both groups, there were few cases with esthetic implications."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
High school students aged 17–20 years **Sampling time frame:** January to September 2017 **Sample size:** 660 (331 exposed and 329 unexposed to fluoridated water) **Sex: N (%):** Boys: 275 (41.7%) **Exclusions:** • Students who had lived in the study area <70% of their lives. • Students with a fixed orthodontic appliance or those with amelogenesis imperfecta **Source of funding / support**	**Method of exposure assessment:** • Fluoride in water by a specific ion electrode (Orion Model 96–09) coupled to the ion analyzer (Orion Star A211, S~ao Paulo, Brazil). **Exposure level(s):** Fluoride levels in: • Fluoridated water: 0.50 to 0.90 ppm • Non-fluoridated water: <0.05 ppm	**Method of outcome ascertainment:** Thylstrup and Fejerskov (TF) index The intra and inter-examiner kappa indexes were 0.87 and 0.85 for dental fluorosis.	Fluorosis prevalence and severity (n, %) Fluorosis absent • Exposed: 195 (58.9%) • Unexposed: 260 (79.0%) Very mild or mild fluorosis: • Exposed: 96 (29.0%) • Unexposed: 55 (16.7%) Moderate fluorosis: • Exposed: 40 (12.1%) • Unexposed: 14 (4.3%) P<0.001 Multivariate logistic regression Very mild or mild fluorosis • Exposed: AOR [adjusted odds ratio] =2.26 (95% CI: 1.54–3.32) • Unexposed: reference • P<0.001 Moderate fluorosis • Exposed: AOR=3.66 (95% CI: 1.93–6.95) • Unexposed: reference	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
NR **Author declaration of interest:** NR			• P<0.001	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants selected using same criteria. Sampling time frame reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Confounders were adjusted for.
Performance	Were experimental conditions identical across study groups?	NA	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in water using a specific ion electrode and ion analyzer
	Can we be confident in the outcome assessment?	++	DF examined using the Thysltrup and Fejerskov criteria
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

McLaren 2022 [16]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Routes of exposures:**	**Outcome(s):** Dental fluorosis	**Statistical analysis:**	• "Although estimates of

Trial Ex. 131.131

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Cross-sectional ["pre-post cross-sectional design with comparison group"] **Country:** Canada **Participants:** Children aged ~7 years (grade 2 schoolchildren) **Sampling time frame:** • 2018-2019 school year • Pre-cessation data (2004/2005 and 2009/2010 [Calgary only]), early post-cessation data (2013/2014) from previous studies **Sample size:** <u>2018-2019</u>	Water fluoridation <u>Fluoride levels in</u> • Fingernails • Water (in water treatment plants) **Method of exposure assessment:** <u>Water fluoridation status</u> • Never exposed to water fluoridation (Calgary) • Always exposed to water fluoridation (Edmonton) <u>Fluoride levels in</u> • Fingernails: Method of analysis not reported; reference to Whitford et al.		• Poisson, Zero-inflated Poisson, or logistic regression (as appropriate) for comparison between Calgary and Edmonton • Difference-in-differences approach to compare trends over time between Calgary and Edmonton **Results:** Prevalence (95% CI), % <u>Note</u>: crude - weighted estimate for the full samples; adjusted - weighted estimate adjusted for covariates; subset - crude weighted estimate for lifelong residents of Calgary or Edmonton who reported usually drinking tap water). <u>Years 2018-2019</u> • Calgary (water fluoridation ceased in 2011): 8.3 (6.6-	fluorosis were higher in Edmonton than in Calgary, it is important to note that nearly all cases (>99%) in both cities were mild, which is in line with national estimates."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Calgary: 1620 • Edmonton: 1402 2004-2005 • Calgary: 380 • Edmonton: 41,749497 2009-2010 • Calgary: 365 • Edmonton: -- 2013-2014 • Calgary: 2084 • Edmonton: 1749 Fingernail clippings (2018/2019) • Calgary: 34 • Edmonton: 31 **Sex: N (%):** NR **Exclusions:** NR **Source of funding / support:** • Research grant from the North American	1999 (Caries Res. 33(6):462-7) who determined fluorides "with the electrode following HMDS-facilitated diffusion". • Water collected in water treatment plants: data from annual water quality reports **Exposure level(s):** Total fluoride in fingernails Mean (95% CI), µg/g • Calgary: 1.1 (0.9 to 1.2)	**Method of outcome ascertainment:** • Tooth Surface Index of Fluorosis [TSIF] criteria. • Dental fluorosis expressed as prevalence: % with TSIF score ≥1 based	10.3 crude; 7.7 (5.9-9.6) adjusted; 6.2 (4.3-8.9) subset. • Edmonton (water fluoridation continues): 19.4 (16.3-22.9) crude; 18.3 (14.9-21.6) adjusted; 18.8 (14.4-24.2) subset. • P<0.05 Changes over time (crude estimates for 2004-05; 2009-10; 2013-14; and 2018-19, respectively) • Calgary (water fluoridation ceased in 2011): 22.6 (18.8, 26.9); 29.1 (24.6, 34.1); 19.9 (17.8, 22.2); 8.3 (6.6-10.3) • Edmonton (water fluoridation continues): 39.8 (37.0, 42.7); no data; 14.1 (11.4, 17.4); 19.4 (16.3-22.9) • Coefficient (95% CI) for difference of changes: −0.1 [−0.2 to −0.1], P<0.001).	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Institutes of Health Research (CIHR) (PJT-156258) • Dr McLaren was supported by an Applied Public Health Chair research award funded by CIHR (Institute of Population & Public Health and Institute of Musculoskeletal Health & Arthritis), the Public Health Agency of Canada, and Alberta Innovates—Health Solutions (CIHR ID CPP-137907) • Dr Weijs was supported by a CIHR Health System Impact Fellowship, 2017-2020 (Award # 403867). **Author declaration of interest:** No COI	• Edmonton: 1.6 (1.3 to 1.8) Median (inter-quartile range), µg/g • Calgary: 1.0 (0.7 to 1.2) • Edmonton: 1.3 (1.3 to 1.5) P<0.0001 Fluoride in water: range (average, if available), µg/L[xxvi] **Calgary** • Bearspaw plant: 2005: 0.6-0.8 2006: 0.7-0.7 2007: 0.6-0.7 2008: 0.7-0.7 2009: 0.7-0.7 2010: 0.7-0.7 **2011: 0.1-0.7**	on the most severe level of fluorosis detected on the central maxillary incisor teeth (permanent teeth only, and only if at least half erupted) • Intra-rater agreement kappa: 0.87 • Inter-rater agreement kappa: 0.77		

[xxvi] Fluoridation of drinking water in Calgary ceased on May 19, 2011. Water fluoride values for year 2011 in Calgary are underlined.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	2012: 0.1-0.1 2013: 0.1-0.2 2014: 0.1-0.3 2015: 0.1-0.1 (0.1) 2016: 0.1-0.1 (0.1) 2017: 0.1-0.2 (0.1) 2018: 0.1-0.2 (0.1) 2019: 0.1-0.3 (0.2) • Glenmore plant: 2005: 0.7-0.8 2006: 0.6-0.8 2007: 0.7-0.7 2008: 0.6-0.7 2009: 0.6-0.8 2010: 0.6-0.9 **2011: 0.1-0.7** 2012: 0.2-0.3 2013: 0.1-0.3 2014: 0.1-0.3 2015: 0.2-0.3 (0.3)			

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	2016: 0.2-0.3 (0.2) 2017: <0.1-0.3 (0.2) 2018: 0.2-0.3 (0.2) 2019: 0.1-0.3 (0.2) **Edmonton** • Rossdale plant: 2005: 0.7-1.0 (0.8) 2006: 0.8-0.9 (0.8) 2007: 0.5-0.9 (0.7) 2008: 0.1-0.9 (0.8) 2009: 0.7-0.9 (0.8) 2010: 0.6-0.8 (0.7) 2011: 0.6-0.8 (0.7) 2012: 0.0-0.8 (0.5) 2013: 0.6-0.8 (0.7) 2014: 0.6-0.9 (0.7) 2015: 0.6-0.8 (0.7) 2016: 0.6-0.8 (0.7) 2017: 0.6-0.8 (0.7) 2018: 0.6-0.8 (0.7)			

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	2019: 0.6-0.8 (0.7) • EL Smith plant: 2005: 0.7-0.9 (0.8) 2006: 0.7-0.9 (0.8) 2007: 0.1-0.9 (0.8) 2008: 0.0-0.8 (0.4) 2009: 0.7-0.8 (0.7) 2010: 0.7-0.8 (0.7) 2011: 0.1-0.8 (0.6) 2012: 0.6-0.8 (0.7) 2013: 0.6-0.8 (0.7) 2014: 0.5-0.9 (0.7) 2015: 0.6-0.8 (0.7) 2016: 0.6-0.8 (0.7) 2017: 0.6-0.8 (0.7) 2018: 0.5-0.8 (0.7) • 2019: <0.1-0.8 (0.5)			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants selected using same criteria. Sampling time frame reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Confounders were adjusted for.
Performance	Were experimental conditions identical across study groups?	NA	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	"We developed sampling weights that accounted for the probability of selection (as per the sampling frame) and the probability of non-response, thus increasing the extent to which our samples resembled the underlying target populations. This approach enabled us to handle missing observations within the framework of our survey sampling approach rather than, for example, having to

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			estimate differences between our samples and the target populations"
Detection	Can we be confident in the exposure characterization?	+	Water fluoridation status: Calgary (fluoridation cessation); Edmonton (still fluoridated). Source of information unclear.
	Can we be confident in the outcome assessment?	++	DF examined using Tooth Surface Index of Fluorosis
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Rani 2022 [17]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** India **Participants:** Children aged 6-12 years **Sampling time frame:** NR **Sample size:** 1262 **Sex: N (%):** Boys: 615 (48.7%) **Exclusions:** • Children who were not continuous	**Exposures** Fluoride levels in • Groundwater **Method of exposure assessment:** Fluoride in water: Ion Selective Electrode Method using ION check 45 m. **Exposure level(s):** Fluoride in groundwater (ppm): 0.532–8.802	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** Dean's Fluorosis Index	**Statistical analysis:** • Descriptive analysis **Results:** Dean's fluorosis index (mean) by level of groundwater fluoride: • Low (<0.7 ppm): 0.62 [1 village] • Optimum (0.7–1.5 ppm): 0.72 to 1.33 [5 villages] • High (1.5-4 ppm): 1.32 to 2.31 [19 villages] • Very high (>4 ppm): 2.62 to 3.34 [5 villages] Correlation between groundwater fluoride and Dean's fluorosis index • r=0.922; p<0.01	• "The risk of dental fluorosis was significantly higher in the areas showing more fluoride content in drinking water." • "There is an urgent need to improve the quality of water and institute de-fluoridation of drinking water in affected areas to lower the burden of dental fluorosis in the community either by making alternative sources available or providing water with an optimal concentration of fluoride."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
residents of the study area since birth **Source of funding / support:** • None **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants selected using same criteria. Sampling time frame not reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	Correlation analyses, t-tests, and Chi-square tests were conducted

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Performance	Were experimental conditions identical across study groups?	NA	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	NR
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in water using Ion Selective Electrode Method
	Can we be confident in the outcome assessment?	++	DF examined using Dean's Fluorosis Index
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Saeed 2022 [18]

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Pakistan **Participants:** Children aged 5-16 years **Sampling time frame:** NR **Sample size:** 148 (118 exposed; 30 controls)	**Exposures** <u>Fluoride levels in</u> • Urine • Groundwater used for drinking **Method of exposure assessment:** • Urinary fluoride by fluoride ion-selective electrode (Hanna, Model HI-522). • Water fluoride: NR	**Outcome(s):** Dental fluorosis Non-verbal intelligence quotient (IQ)	**Statistical analysis:** • Chi-square test • Independent samples t-test • Spearman's rank correlation (according to the Methods section); Pearson correlation (according to the title of table 2) • Linear regression (Backward stepwise) **Results:** **Dental fluorosis** <u>Frequency and severity of dental fluorosis, n (%)</u> Control group • Normal: 28 (94.0) • Questionable: 2 (6.0) Exposed group	• "Mean urinary concentrations of As … and F- … as well as the frequency of dental fluorosis were found elevated among the exposed group." • "The cases of children with lower IQ were observed high in the exposed group." • "… it was revealed that variations in dental fluorosis and IQ levels were more significantly associated with F-exposure compared to As."

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: N (%): Boys: 112 **Exclusions:** • Non-permanent residents in the study area • Drinking water source other than groundwater **Source of funding / support:** None **Author declaration of interest:** No COI	**Exposure level(s):** <u>Water fluoride (mg/L)</u> • Control group: 0–0.5, mean 0.15 (SD 0.13) • Exposed group: 0.10–15.80, mean 5.64 (SD 3.52) • P=0.000 <u>Urinary fluoride (mg/L)</u> • Control group: 0.40–0.75, mean 0.24 (SD 0.15) • Exposed group: 0.47–14.56, mean 3.27 (SD 2.60) • P=0.000	**Method of outcome ascertainment:** • Dental fluorosis: Dean's index • Non-verbal IQ: Wechsler scale of intelligence (WISC-IV)	• Normal: 0 • Questionable: 16 (13.55) • Very mild: 22 (18.65) • Mild: 21 (17.80) • Moderate: 25 (21.19) • Severe: 34 (28.81) <u>Correlation analysis</u> Water fluoride and urinary fluoride: r=0.224; p=0.006 Water fluoride and dental fluorosis: r=0.380; p=0.000 Urinary fluoride and dental fluorosis: r=0.721; p=0.000 <u>Linear regression analysis</u> Fluoride in urine as an independent variable: • β=0.38 (SE 0.03) [unstandardized] • β=0.66 [standardized]; p=0.00	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Other independent variables in the model: gender, family economic status, arsenic in urine. Model summary: F = 49.00; adjusted R^2=0.57; p=0.000 **Non-verbal intelligence quotient (IQ)** <u>IQ score</u> Control group: 80.25–127.75; mean 100.93 (SD 13.1) Exposed group: 63.97–127.31; mean 97.26 (SD 15.39)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			P=0.233 <u>Correlation analysis</u> Water fluoride and urinary fluoride: r=0.224; p=0.006 Water fluoride and IQ score: r=-0.034; p=0.683 Urinary fluoride and IQ score: r=-0.655; p=0.000 Dental fluorosis and IQ score: r=-0.552; p=0.000 <u>Note</u>: Levels of fluoride significantly correlated with arsenic levels. <u>Linear regression analysis</u>	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Fluoride in urine as an independent variable: • β=-3.45 (SE 0.50) [unstandardized] • β=-0.60 [standardized] • P=0.00 Other independent variables in the model: age, gender, parental education, dental fluorosis. Model summary: F = 29.64; adjusted R^2=0.49; p=0.000 <u>Intelligence level vs mean (SD) water fluoride (WF), urinary fluoride (UF), water arsenic (WA) and urinary arsenic (UA)</u>	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Superior (IQ score ≥130): no participants with this level Above average (IQ score 120-129) • WF: 1.96±2.77 mg/L • UF: 0.54±0.59 mg/L • WA: 0.02±0.05 mg/L • UA: 0.68±1.54 mg/L High Average (IQ score 111-119) • WF: 4.60±4.40 mg/L • UF: 1.20±0.80 mg/L • WA: 0.12±0.15 mg/L • UA: 2.71±1.78 mg/L Average (QI score 90-100) • WF: 4.3±3.99 mg/L • UF: 1.99±1.28 mg/L • WA: 0.16±0.22 mg/L • UA: 3.13±2.29 mg/L	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Low average (IQ score 80-89) • WF: 3.84±3.63 mg/L • UF: 3.61±2.84 mg/L • WA: 0.14±0.16 mg/L • UA: 2.65±1.80 mg/L Borderline (IQ score 70-79) • WF: 6.19±4.59 mg/L • UF: 7.13±2.62 mg/L • WA: 0.15±0.09 mg/L • UA: 3.75±1.26 mg/L Retarded (IQ score <70) • WF: 4.92±3.46 mg/L • UF: 8.10±5.84 mg/L • WA: 0.17±0.28 mg/L • UA: 3.50±0.81 mg/L	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants selected using same criteria. Time frame not reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	"Multiple linear (Backward stepwise) regression models were used to examine the associations between (a) IQ level, MDA, SOD, CAT, GR, and dental fluorosis with independent variables including age, gender, economic status, parent education, As and F- in the urine." (p. 3936)
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	NR
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in urine using fluoride ion-selective electrode

Risk of bias assessment					
Bias domain	***Criterion***	***Response***			
	Can we be confident in the outcome assessment?	+	IQ measured using the Wechsler scale of intelligence (WISC-IV). Unclear blinding	++	Dental fluorosis assessed using Dean's Index.
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Tawfik 2022 [19]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Egypt	**Exposures:** <u>Fluoride levels in:</u> • Groundwater	**Outcome(s):** • Dental fluorosis	**Statistical analysis:** • Pearson's correlation	• "Correlation between fluorosis status and fluoride level in drinking water was performed by using Pearson`s

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: 7-14 years old children with no tooth fillings or braces, who live in the same region since birth **Sampling time frame:** December 2020-March 2021 **Sample size:** 202 **Sex: N (%):** NR **Exclusions:** • Teeth covered with filling or braces • Parents or children who refused to join the study. • Ethical Consideration **Source of funding / support:** • Self-funded	**Method of exposure assessment:** • Water analysis was conducted in the National Research Centre (method unreported). **Exposure level(s):** • <u>Fluoride Levels in drinking water:</u> 7.5-9.5, mean 8mg/L	**Method of outcome ascertainment:** • Modified Dean's Index	**Results:** • <u>Dental Fluorosis – Modified Dean's Index:</u> Mean ± SD: 2.31 ±0.94 • <u>Dental Fluorosis (%)</u> Normal: 0% Questionable: 0% Very Mild: 19.8% Mild: 40% Moderate: 30% Severe:9.9%	correlation coefficient and revealed strong, positive, significant correlation." • "Nubian children recorded moderate and severe fluorosis status score because on analysis of their drinking water, their result showed that mean fluoride level was 8 mg/L." •

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected using the same criteria and during the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, the study reported on reasons for exclusion of study participants (teeth covered with fillings or braces, parents or children who refused to join the study, and other “undeclared” ethical considerations)
Detection	Can we be confident in the exposure characterization?	+	Water analysis was conducted in the National Research Centre (method unreported).

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Can we be confident in the outcome assessment?	++	Yes, all participants were “clinically” examined for the outcome (DF), using Modified Dean’s Index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Thilakarathne 2022 [20]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Sri Lanka	**Exposures** Fluoride level in • Drinking water	**Outcome(s):** Dental fluorosis	**Statistical analysis:** • Chi square test for trends	• “The prevalence of dental fluorosis was high and it increased with the increase in the fluoride content in the

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Children aged 15 years **Sampling time frame:** NR **Sample size:** 1040 [total] 989 [analytical] **Sex: N (%):** Boys: 45.2% of the total sample **Exclusions:** • Children who had not resided in the study area since birth • Children with learning difficulties, wearing fixed orthodontic appliances and those who were absent on the day of the oral examination	**Method of exposure assessment:** • Fluoride content in water by spectrophotometry **Exposure level(s):** • Fluoride levels in water: 0.0-1.9 mg/L	**Method of outcome ascertainment:** Thylstrup and Ferjeskov (TF) index	**Results:** <u>Prevalence of dental fluorosis</u> • TF score > 0: 51.7% • TF score > 1: 41.5% • TF score > 2: 20.5% <u>Prevalence of dental fluorosis by TF score</u> • TF0 [normal]: 48.3% • TF1: 10.2% • TF2: 20.9% • TF3: 11.8% • TF4: 5.9% • TF5: 2.3% • TF6: 0.5% <u>Association between fluoride level in drinking water and prevalence of dental fluorosis (TF score>0)</u> • Water fluoride <0.3 mg/L: 42.3% • Water fluoride 0.31-0.6 mg/L: 62.8%	drinking water source."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: Research Grant (RG/2016/84/D) from the University of Peradeniya **Author declaration of interest:** NR			• Water fluoride 0.61-0.9 mg/L: 70.1% • Water fluoride >0.9 mg/L: 88.9 • p (Chi sq for trend) <0.001	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants selected using same criteria. Sampling time frame not reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	Chi-square test for trends was conducted

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Performance	Were experimental conditions identical across study groups?	NA	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in water using spectrometry
	Can we be confident in the outcome assessment?	++	DF examined using the Thysltrup and Fejerskov criteria
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Al-Omoush 2021 [21]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** Jordan **Participants:** • School children residing in Ruwaished (age 15.3 +/- 1.4 years) and Kuraymah (age 16.1 +/- 1.3 years)	**Exposures:** <u>Fluoride level in</u> Drinking water samples from wells **Method of exposure assessment:** Fluoride-ion selective electrode coupled with ionalyzer **Exposure level:** Average fluoride level in water (ppm) <u>Ruwaished</u> • 1.38	**Outcome(s):** Dental fluorosis prevalence and severity **Method of outcome ascertainment:** Dean's index used to determine dental fluorosis severity	**Statistical analysis:** Statistical significance at p = 0.05 **Results:** Frequency (%) distribution of dental fluorosis by Dean's Fluorosis Index in Kuraymah <u>Normal</u> • N = 10 / 141 (7.1%) <u>Very mild</u> • N = 13 / 141 (9.2%) <u>Mild</u> • N = 21 / 141 (14.9%)	"This study concluded that higher fluorosis incidence and severity were present in the higher-altitude location (Ruwaished). Moreover, this study also indicated that … the preventive management of dental fluorosis should be directed to de-fluoridation of drinking water in

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: NR **Sample size:** • Ruwaished: 100 • Kuraymah: 141 **Sex: N (%):** • Ruwaished: Men: 60 (60%) • Kuraymah: Men: 85 (39.7%) **Exclusions:** NR **Source of funding / support:** NR	Kuraymah • 1.10		Moderate • N = 51 / 141 (36.2) Severe • N = 46 / 141 (32.6) Frequency (%) distribution of dental fluorosis by Dean's Fluorosis Index in Ruwaished Normal • N = 0 / 100 (0%) Very Mild • N = 9 / 100 (9%) Mild • N = 19 / 100 (19%) Moderate	endemic areas." (p. 707 – 708)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI			• N = 22/100 (22%) <u>Severe</u> • N = 50 / 100 (50%)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR

Risk of bias assessment			
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water wells using a combination of F-selective electrode (Orion model 960900), coupled with an ionalyzer (Orion mode l901, Cambridge, U.S.A.)
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was done by trained and calibrated examiners (no professional information reported), using Dean's fluorosis index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Ayele 2021 [22]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional (part of an ongoing cohort study in the Ethiopian Rift Valley)	**Exposures:** Fluoride levels in Ground water (community wells) **Method of exposure assessment:**	**Outcome(s):** • Skeletal fluorosis • Joint pain • Neurological manifestations (headache, paresthesia, loss of appetite, constipation, and fatigue)	**Statistical analysis:** • Descriptive analysis • Univariate analysis • Multivariable regression **Results:** • At least one clinical sign of skeletal fluorosis was observed in 54.4% of the study participants. • For every 1 mg/L increment of fluoride in	"The study demonstrates high prevalence of neuro-medical manifestations of fluorosis in population living in the Main Ethiopian Rift valley. Fluoride concentration in

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Ethiopia **Participants:** Persons aged 10–70 years old, selected at random from those who lived and used water wells from 23 rural villages **Sampling time frame:** Two sampling periods (between 2018 and 2019)	The ion-selective electrode (ISE) **Exposure level:** • Mean concentration: 6.8 ± 4.3 mg/L • Range: 0.3–15.5 mg/L	**Method of outcome ascertainment:** A comprehensive physical examination with emphasis on neurological examination, conducted by two certified neurologists	drinking water, the odds of skeletal fluorosis increased by 1.15 upon adjustment for age and selected clinical variables [Adjusted OR 1.15, 95%CI (1.04–1.27); p = 0.006]. • Signs of crippling fluorosis were observed in small proportion (1.6%) of participants. • Fluoride concentration in drinking water and joint pain were found to be independent predictors of skeletal fluorosis. • Headache and joint pain reported by 67.1% and 56.3% of participants as the most common neurological manifestation, and skeletal fluorosis symptom, respectively. • The mean fluoride level was higher for those individuals who reported	drinking water and joint pain were independent predictors of fluorosis.”

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size: 316 **Sex (N):** Men: 176 (55.7%) **Exclusions:** NR **Source of funding / support:** NIEHS's career development grant			paresthesia compared to those with no-paresthesia. • Loss of appetite, constipation, and fatigue were reported by 48.0%, 45.6%, and 56.6% of the participants, respectively. • Individuals who reported headache are most likely exposed to higher fluoride concentrations in drinking water compared to those reported no-headache ($p<0.001$).	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified using the same method of ascertainment, recruited within the same time frame, and using the same criteria.

Risk of bias assessment					
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Yes, it accounted for age and select clinical covariates. The populations were reported as fairly homogenous with similar ethnicity, economic, and nutritional status.		
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable		
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable		
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (participation in the pilot testing of the field questionnaire)		
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the ion selective electrode method.		
	Can we be confident in the outcome assessment?	++	Yes, the outcome (skeletal fluorosis) was assessed using comprehensive physical examination	–	The outcome (multiple neurological symptoms) was assessed using face-to-face interviews by

Risk of bias assessment					
			by two certified neurologists. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.		trained field enumerators (graduate students and nurses / medical doctors). Comprehensive physical examination with a focus on neurological signs was conducted by two certified neurologists. Lack of blinding of outcome might have appreciably biased the results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome (skeletal fluorosis) discussed in the methods was presented in results section with adequate	++	Yes, the primary outcome (medical conditions grouped as neurological) were discussed in methods was presented in

Risk of bias assessment					
			level of detail for data extraction		results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Cao 2021 [23]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional	**Exposures:** Fluoride levels in: • Drinking water • Urine	**Outcome(s):** • Dental fluorosis	**Statistical analysis:** • Rate or composition ratio • Chi-square test	• "The prevalence rate of dental fluorosis among children in each

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: China **Participants:** Dental fluorosis: Children aged 8-<13 years Urinary fluoride: Age 25 and over **Sampling time frame:** June 2017- June 2019 **Sample size:** Dental fluorosis: 1346 Urinary fluoride: 450 **Sex:** Boys: 50% **Exclusions:**	**Method of exposure assessment:** • The fluorine content in water was determined by "Standard Test Method for Drinking Water" (GB/T5750.5-2006). • Determination of Urinary Fluorine Content Fluoride Determination Ion Selective Electrode Method»(WS/T89-2015) **Exposure level(s):** • Drinking water Fluoride range:	**Method of outcome ascertainment:**	**Results: CHI SQURE tests add** • Detection rates for dental fluorosis: (P:0.357) 2017: 1.75% (7/401) 2018: 1.40% (7/500) 2019: 0.67% (3/445) .062, P=0.357 Overall, 2017-2019: 1.26% (17/1 346) Total DF Index: 0.03 • Dental fluorosis cases: Suspicious: 35(2.60%) Very Mild: 12 (0.89%) Mild: 5 (0.37%) Moderate: 0 Severe:0 • Highest DF in Minhou County	diseased area is <30%." • "Results indicate reduction of fluoride in Fuzhou county, concluded in reduction of endemic dental fluorosis (with very mild and mild cases)." • "There is no statistically significant difference in the detection rate of dental fluorosis among children in each year and among children of different age. groups"

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Demolition victims of Yinpu Natural Village **Source of funding / support:** NR **Author declaration of interest:** No COI	0.05-0.76 mg/L • Urinary Fluoride 0.04 - 3.76 mg/L (Geometric Mean: 0.8 mg/L) Upper limit of normal value is ≤1.60 mg/L.	• Dean's index [by Dental fluorosis index (fluorosis community index, FCI)] • The grading of dental fluorosis was carried out according to "Diagnosis of Dental Fluorosis" (WS/T208-2011).	Detection rates/years: 2017: 21.21% (7/33) 2018: 17.95% (7/39) 2019: 13.04% (3/23) P=0.7	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe, according to the same criteria and from the same eligible population.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from drinking water samples that were collected from the local source of water supply in each village. Fluoride concentrations were determined using the Ion Selective Electrode Method (WS/T89-2015)
	Can we be confident in the outcome assessment?	++	The diagnosis of DF was assessed by trained investigators using Dean's fluorosis index. Blinding of exposure status may have not significantly biased the assessment
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Dong 2021 [24]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross sectional **Country:** United States **Participants:** US children and adolescents 6–19 years old (NHANES survey) **Sampling time frame:**	**Exposures:** <u>Fluoride levels in</u> • Drinking water • Serum **Method of exposure assessment:** <u>Water fluoride:</u> Measured electrometrically using the ion-specific electrode (CDC, 2017a). <u>Serum fluoride:</u> Measured in duplicate using the same sample	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** Assessment of dental fluorosis conducted by certified dentists, according to the Dean's Fluorosis Index (DFI) and assigned one of the DFI disease severity categories, based on the area of the tooth surface with visible fluorosis and presence of pitting (NHANES	**Statistical analysis:** • Binary logistic regression analyses were used to determine the association between fluoride exposure and dental fluorosis, • Controlled for age, sex, race/ethnicity, BMI categories, the ratio of family income to poverty and six-month time period when surveyed. **Results:** • The rate of fluoride concentration in water above the recommended level of 0.7 mg/L was 25%, but the prevalence of dental fluorosis was 70%.	"Even low level of water or plasma fluoride exposure was associated with increased risk of dental fluorosis."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
2015-2016 **Sample size:** 2098 children and adolescents **Sex:** Men: 1,054 (50.24%) **Exclusions:** Survey respondents with missing any of the fluoride measurements, dental fluorosis assessment or complete data for all	and the average of two results was employed (Centers for Disease Control and Prevention, 2017b). **Exposure level:** <u>Water fluoride (mg/L): Mean (SD)</u> All: 0.46 (0.40) Men: 0.48 (0.41) Women: 0.47 (0.38) Children: 0.52 (0.44) Adolescents 0.43 (0.35)	Dental Examiners Procedures Manual, 2016).	• Binary logistic regression adjusted for covariates showed that higher water fluoride concentrations (0.31–0.50, 0.51–0.70, > 0.70 compared 0.00–0.30) were associated with higher odds of dental fluorosis ○ *<u>0.31–0.50:</u> OR=1.48 (1.13–1.96), p = 0.005* ○ *<u>0.51–0.70:</u> OR=1.92, (1.44–2.58, p < 0.001* ○ <u>> 0.70:</u> *OR=2.30 (1.75–3.07), p < 0.001* The pattern of regression between plasma fluoride and dental fluorosis was similar.	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
covariates and outcomes. **Source of funding / support:** • Fundamental Research Funds for the Central Universities (No. 3332019030) • Youth Program of Peking Union Medical College Hospital Foundation (No. PUMCH 201910847), • National Natural Science Foundation of China (81703198). **Author declaration of interest:** No COI	Plasma fluoride (μmol/L): Mean (SD) All: 0.35 (0.22) Men: 0.36 (0.19) Women: 0.34 (0.25) Children: 0.38 (0.24) Adolescents: 0.32 (0.20)			

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected using the same criteria and during the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, sex, race, BMI, family income to poverty, and six month time period when surveyed
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water (the ion-specific electrode test) and serum (the ion-specific electrode and hexamethyldisiloxane [HMDS] test).
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was consistently measured by two dentists using Dean's Fluorosis Index, in accordance with the NHANES Dental Examiners Procedures Manual, 2016. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were	++	None identified

Risk of bias assessment				
	appropriate and researchers adhered to the study protocol)?			

Du 2021 [25]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional	**Exposures:** Fluoride levels in • Urine **Method of exposure assessment:** • Urinary fluoride (UF): the ion-selective	**Outcome(s):** Thyroid hormone dysfunction: • Total triiodothyronine (TT3) • Total thyroxine (TT4) • Thyroid-stimulating hormone (TSH)	**Statistical analysis:** • Linear regression **Results:** **Tvol (cm3)** • All	• "Fluoride exposure can elevate the Tvols of school-age children, especially in boys, and high levels of iodine may alleviate this effect to some extent"

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: China **Participants:** Children aged 7–12 years old **Sampling time frame:** 2017 **Sample size:** 446 **Sex (N):** Boys: 237 (53.1%)	electrode method (Shanghai Exactitude Instrument, Shanghai, China). **Exposure level:** Urinary fluoride (mg/l) All: 1.45 ± 0.88 Boys: 1.43 ± 0.89 Girls: 1.48 ± 0.87 t/x^2: 0.490 P-value: 0.624	• Tvols (thyroid volumes) **Method of outcome ascertainment:** • Clinical examination conducted by skilled medical professionals • Serum TT3, TT4, TSH: radiation immunoassay using the auto biochemical analyzer (Cobas C501, Roche Diagnostics, Basel, Switzerland) • The B-mode ultrasound was performed to assess thyroid volumes (Tvols).	β (95% CI): 0.22 (0.14, 0.31), p-value: < 0.001 • Boys β (95% CI): 0.34 (0.20, 0.48), p-value: < 0.001 • Girls β (95% CI): 0.14 (0.03, 0.24), p-value: 0.011 • Interaction β (95% CI): − 0.15 (− 0.30, − 0.01), p-value: 0.038 **TT4 (nmol/l)** • All β (95% CI): 1.44 (− 1.28, 4.16), p-value: 0.297 • Boys:	• No significant difference between boys and girls in age, maternal education, UCr, UF, UI, Tvol, TT4, and TT3. • BMI in boys was significantly higher than that in girls (P < 0.05), • TSH concentration was significantly lower in boys than girls (P < 0.001) • Tvols increased by 0.22 (95% CI: 0.14, 0.31) cm^3 with each standard deviation increment of UF. • Tvols in boys were more susceptible to

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: • Children with a history of the thyroid-related diseases (such as hyperthyroidism, hypothyroidism, thyroid nodules, thyroid goiters, and Hashimoto's thyroiditis) • Children with urinary iodine < 100 μg/l) **Source of funding / support:** • National Natural Science Foundation of China • The Henan Department of Science and Technology, China			β (95% CI): 2.13 (− 2.89, 7.14), p-value: 0.404 • Girls β (95% CI): 0.89 (− 2.27, 4.04), p-value: 0.580 • Interaction β (95% CI): − 1.46 (− 6.17, 3.24), p-value: 0.542 **TT3 (nmol/l)** • All β (95% CI): − 0.05 (− 0.10, 0.01), p-value: 0.087 • Boys	fluoride exposure than those in girls • Tvols of children with high urinary iodine are less susceptible to fluoride exposure (P for interaction < 0.05). • TT3 levels were negatively related to UF concentrations at moderate urinary iodine levels (≤ 300 μg/l).

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Zhengzhou University **Author declaration of interest:** No COI			β (95% CI): − 0.08 (− 0.17, 0.01), p-value: 0.072 • Girls β (95% CI): − 0.03 (− 0.10, 0.04), p-value: 0.381 • Interaction β (95% CI): 0.01 (− 0.08, 0.10), p-value: 0.795 **TSH (μIU/ml)** • All-β (95% CI): − 0.07 (− 0.20, 0.07) • p-value: 0.316 • Boys-β (95% CI): 0.06 (− 0.04, 0.17) • p-value: 0.229 • Girls-β (95% CI): − 0.15 (− 0.38, 0.08) • p-value: 0.202	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Interaction-β (95% CI): − 0.11 (− 0.33, 0.12) • p-value: 0.363	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected using the same criteria and during the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, gender, BMI, maternal education, urinary creatinine, urinary iodine and urinary fluoride
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water (the ion-specific electrode test) and serum (the ion-specific electrode and hexamethyldisiloxane [HMDS] test).
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was consistently measured by two dentists using Dean's Fluorosis Index, in accordance with the NHANES Dental Examiners Procedures Manual, 2016. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were	++	None identified

Risk of bias assessment			
	appropriate and researchers adhered to the study protocol)?		

Farmus 2021 [26]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cohort study **Country:** Canada	**Exposures:** <u>Fluoride levels in</u> • Maternal urine (MUF): prenatal exposure • Children urine (CUF): Childhood exposure **Method of exposure assessment:**	**Outcome(s):** • Intelligence at 3 to 4 years of age **Method of outcome ascertainment:** • Assessed by trained research assistants using the Wechsler Preschool and Primary	**Statistical analysis:** • Generalized estimating equations (GEE) used to assess association of interest • Statistical significance at α = 0.05 for two-tailed test • Pint: interaction between exposure timing and fluoride level was assessed	"Our results suggest the associations of prenatal and postnatal fluoride exposure with cognitive development may be modified by sex,

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Mother-child pairs in the Maternal-Infant Research on Environmental Chemicals (MIREC) study **Sampling time frame:** 2008 - 2011 **Sample size:** 596 **Sex N (%):** Female: 305 (51.2%)	• Specific gravity used to adjust for urinary dilution • Prenatal exposure acquired by taking the mean trimester-specific fluoride level • Childhood exposure acquired by measuring fluoride levels between 1.9 and 4.4 years of age • Infant fluoride intake (IFI) estimated over first year of life using water fluoride level and formula-feeding duration **Exposure level:** Median (range) fluoride levels <u>MUF T1 (mg/L)</u> • 0.31 (0.01 – 4.29) <u>MUF T2 (mg/L)</u>	Scale of Intelligence-III (WPPSI-III) • Specific outcome measures include: Performance IQ (PIQ), Verbal IQ (VIQ), and Full-Scale IQ (FSIQ)	• Adjusted covariates: maternal education, maternal race, total HOME score, age at urine sampling, and prenatal second-hand smoke **Results:** Change (95% CI) in age-normed in FSIQ scores per unit increase in standardized fluoride exposure <u>Males</u> • MUF: -1.86 (-3.22, -0.49) • IFI: -0.01 (-1.67, 1.65) • CUF: 0.07 (-1.66, 1.80) • Pint: .012 <u>Females</u> • MUF: -0.23 (-2.06, 1.60) • IFI: -0.72 (-2.34, 0.89) • CUF: -0.41 (-2.07, 1.24)	though further replication of this finding is needed. These results indicate that it is important to balance the risks of fluoride exposure during early brain development with its potential to prevent caries, especially for pregnant women and infants.” (p. 7)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: • Fetal abnormalities • Medical complications • Gestational illicit drug use **Source of funding / support:** • National Institute of Environmental Sciences (NIEHS) • Chemicals Management Plan at Health Canada, the Ontario Ministry of the Environment, and the North American Institutes for Health Research	• 0.37 (0.03 – 5.28) <u>MUF T3 (mg/L)</u> • 0.49 (0.08 – 5.56) <u>IFI (mg F)</u> • 0.09 (0.00 – 0.61) <u>CUF (mg/L)</u> • 0.39 (0.05, 2.89)		• Pint: 0.77 <u>Overall</u> • MUF: -1.28 (-2.37, -0.18) • IFI: -0.38 (-1.53, 0.78) • CUF: -0.18 (-1.38, 1.02) • Pint: -0.23 Change (95% CI) in age-normed in PIQ scores per unit increase in standardized fluoride exposure <u>Males</u> • MUF: -3.01 • IFI: -1.45 (-3.40, 0.49) • CUF: -1.49 (-3.50, 0.53) • Pint: 0.01 <u>Females</u> • MUF: -1.18 (-3.32, 0.96) • IFI: -2.71 (-4.59, -0.83) • CUF: -1.53 (-3.45, 0.39) • Pint: 0.01 <u>Overall</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI			• MUF: -2.36 (-3.63, -1.08) • IFI: -2.11 (-3.45, -0.76) • CUF: -1.51 (-2.90, -0.12) • Pint: <0.001 Change (95% CI) in age-normed in VIQ scores per unit increase in standardized fluoride exposure <u>Males</u> • MUF: -0.25 (-1.57, 1.07) • IFI: 1.22 (-0.39, 2.83) • CUF: 1.61 (-0.06, 3.29) • Pint: 0.12 <u>Females</u> • MUF: 0.87 (-0.91, 2.64) • IFI: 1.31 (-0.25, 2.87) • CUF: 0.63 (-0.98, 2.23) • Pint: 0.30 <u>Overall</u> • MUF: 0.15 (-0.91, 1.20) • IFI: 1.27 (0.15, 2.39)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• CUF: 1.10 (-0.06, 2.26) • Pint: 0.04 Change (95% CI) in FSIQ scores per unit increase (0.5 mg/L MUF; 0.1 mg/day IFI; 0.5 mg/L CUF) in fluoride exposure <u>Males</u> • MUF: -2.48 (-4.30, -0.66) • IFI: -0.01 (-1.25, 1.24) • CUF: 0.09 (-2.10, 2.28) • Pint: 0.12 <u>Females</u> • MUF: -0.31 (-2.76, 2.14) • IFI: -0.54 (-1.75, 0.66) • CUF: -0.52 (-2.62, 1.58) • Pint: 0.77 <u>Overall</u> • MUF: -1.71 (-3.17, -0.24) • IFI: -0.28 (-1.15, 0.58) • CUF: -0.23 (-1.75, 1.29) • Pint: 0.23	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Change (95% CI) in PIQ scores per unit increase (0.5 mg/L MUF; 0.1 mg/day IFI; 0.5 mg/L CUF) in fluoride exposure <u>Males</u> • MUF: -4.02 (-6.15, -1.89) • IFI: -1.09 (-2.54, 0.37) • CUF: -1.89 (-4.44, 0.67) • Pint: 0.01 <u>Females</u> • MUF: -1.58 (-4.43, 1.28) • IFI: -2.03 (-3.43, -0.63) • CUF: -1.94 (-4.37, 0.50) • Pint: 0.01 <u>Overall</u> • MUF: -3.15 (-4.85, -1.44) • IFI: -1.58 (-2.59, -0.57) • CUF: -1.91 (-3.68, -0.15) • Pint: <0.001	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Change (95% CI) in VIQ scores per unit increase (0.5 mg/L MUF; 0.1 mg/day IFI; 0.5 mg/L CUF) in fluoride exposure <u>Males</u> • MUF: -0.34 (-2.10, 1.43) • IFI: 0.92 (-0.29, 2.12) • CUF: 2.05 (-0.08, 4.16) • Pint: 0.12 <u>Females</u> • MUF: 1.16 (-1.22, 3.53) • IFI: 0.98 (-0.19, 2.15) • CUF: 0.79 (-1.24, 2.82) • Pint: 0.30 <u>Overall</u> • MUF: 0.20 (-1.22, 1.61) • IFI: 0.95 (0.11, 1.79) • CUF: 1.39 (-0.08, 2.86) • Pint: 0.04	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Sensitivity analysis where influential mother-child dyads were removed was conducted • Association of MUF and FSIQ in boys became weaker and not statistically significant • No change in status of statistical significance for other associations tested	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	"We used data from the Maternal-Infant Research on Environmental Chemical (MIREC) longitudinal cohort, which recruited 2001 pregnant women between 2008 and 2011. Women were recruited from prenatal clinics if they were at

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			least 18 years old, less than 14 weeks gestation, and spoke English or French. Exclusion criteria included fetal abnormalities, medical complications, and illicit drug use during pregnancy; further details have been previously described" (p. 2)
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	"Covariates include maternal education, maternal race, total HOME score, age at urine sampling, and prenatal second-hand smoke" (p. 5)
Performance	Were experimental conditions identical across study groups?	N/A	NA
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	NA
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided. "Our sample included 601 mother-child dyads who completed the follow-up phase of the study (MIREC-Child Development Plus) when children's neurodevelopmental testing was conducted at 3–4 years of age. Data from five mother-child dyads were excluded due to the mothers' declining prenatal and birth data collection (i.e., trimester fluoride exposures, demographic information, covariates, and offspring date of birth), leaving N = 596 mother-child dyads for our full analytic sample (Fig. 1). Other mother-child pairs

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			missing some data on fluoride exposure, outcomes, or covariates were retained due to the flexibility of GEE to incorporate missing data. On outcomes and covariates, no more than 4.6% of data was missing (M = 1.08, range 0–4.6)." (p. 2)
Detection	Can we be confident in the exposure characterization?	++	"Urinary fluoride concentrations were analyzed using a modification of the hexamethydisiloxane"
	Can we be confident in the outcome assessment?	++	"Trained research assistants assessed children's intellectual abilities at the age of 3–4 years using the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III; North American norms; Wechsler, 2002). Outcomes included Performance IQ (PIQ), a measure of nonverbal reasoning, Verbal IQ (VIQ), a measure of verbal reasoning and comprehension, and Full-Scale IQ (FSIQ), a measure of overall intellectual ability. Examiners administered the WPPSI between 2012 and 2015, prior to proposing our fluoride research; examiners are therefore considered blinded to exposure status."
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in methods were reported in the results

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Fernandes 2021 [27]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Brazil **Participants:** Children aged 6-12 years **Sampling time frame:** April-September 2019 **Sample size:**	**Exposures** Fluoride levels in • Water collected from school water fountains **Method of exposure assessment:** • Water fluoride: combined ion-specific fluoride electrode (ORION—	**Outcome(s):** Dental fluorosis	**Statistical analysis:** • Chi-square test • Fisher's exact test **Results:** Group I (water fluoride ≤0.7 ppm): • Fluorosis absent: 306 (63.1%) children. • Fluorosis present: 179 (36.9%) children	• The authors pointed to the high prevalence of dental fluorosis among children exposed to water fluoride ≤0.7 ppm, which may be "an indication of other sources of fluoride (F-toothpaste 1500 ppm) in this region, which was previously observed in other studies".

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
610 **Sex: N (%):** Boys: 329 (53.9%) **Exclusions:** • Children who used a fixed orthodontic appliance or had reading difficulties, tooth malformation (such as amelogenesis imperfecta, dentinogenesis imperfecta, or dentinal dysplasia) **Source of funding / support:** • NR **Author declaration of interest:** No COI	9409BN) and a reference electrode (900200) connected to an ion analyser 710 A (ORION) **Exposure level(s):** Water fluoride (ppm): 0.06-1.98 Group I (≤0.7): 485 children Group II (>0.7): 125 children, including: • 0.7-1.0: 111 children • >1.0-1.98: 14 children	**Method of outcome ascertainment:** Thysltrup and Fejerskov criteria	Group II (water fluoride >0.7 ppm): • Fluorosis absent: 69 (55.2%) children. • Fluorosis present: 56 (44.8%) children P=0.10 Fluorosis absent: OR=1.02 (95% CI: 0.983-1.168) Fluorosis present: 0.77 (0.565-1.055)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants selected using same criteria. Sampling time frame reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	NA	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided
Detection	Can we be confident in the exposure characterization?	++	"a fluoride concentration mapping of the school water supplies was prepared, and water fountains were sampled and analysed using a combined ionspecific fluoride electrode (ORION—9409BN) and a reference electrode (900200) connected to an ion analyser 710 A (ORION)." (p. 476)

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Can we be confident in the outcome assessment?	++	DF examined using the Thysltrup and Fejerskov criteria
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Helte 2021 [28]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposures:** Fluoride levels in • Water • Diet	**Outcome(s):** Bone mineral density and fracture incidence	**Statistical analysis:** • Spearman's rank correlational (rho). • Multivariable linear regression.	"In this cohort of postmenopausal women, the risk of fractures was

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Cohort study [clinical sub-cohort of The Swedish Mammography Cohort (SMC)] **Country:** Sweden **Participants:** All SMC participants who were <85 years of age and residing in the city of Uppsala or nearby surrounding areas	• Urine **Method of exposure assessment:** • Tap water: Geological Survey of Sweden, and the Swedish Water and Wastewater Association), • Food: Swedish National Food Agency, U.S. Department of Agriculture's National Fluoride Database of Selected Beverages and Foods • Tea: scientific literature), • Urine: ion-selective electrode (Combined ISE F 800 DIN; WTW; Xylem Analytics Germany GmbH)).	in postmenopausal women **Method of outcome ascertainment:** • BMD: measured at the lumbar spine and femoral neck using dual energy X-ray absorptiometry (DXA; Lunar Prodigy; Lunar Corp.) • Bone fractures: National Patient Register (NPR)	**Results:** • At baseline: ○ Mean urinary fluoride: 1.2 mg/g creatinine (± 1.9) ○ mean dietary intake was 2:2 mg/d (± 0.9) • During follow-up: ○ 850, 529, and 187 cases of any fractures, osteoporotic fractures, and hip fractures, respectively, were ascertained. • Baseline BMD was slightly higher among women in the highest vs. lowest tertiles of exposure. • Fluoride exposures were positively associated with incident hip fractures, with multivariable-adjusted	increased in association with two separate indicators of fluoride exposure. Our findings are consistent with RCTs and suggest that high consumption of drinking water with a fluoride concentration of ~1 mg=L may increase both BMD and skeletal fragility in older women"

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: Baseline: 2004-2009 Follow-up: 2017 **Sample size:** 4,306 **Sex (N):** Women only (100%) **Exclusions:** • Women who completed a short version of the FFQ • With incomplete FFQ data	**Exposure level:** • Water: ≤1 mg/L • Mean urinary fluoride at baseline: 1.2 mg/g creatinine (0.1–7.3 mg/g creatinine) • Mean estimated dietary fluoride intake: 2.2 mg/d (0.3–8.4 mg/d).		hazard ratios of 1.50 (95% CI: 1.04, 2.17) and 1.59 (95% CI: 1.10, 2.30), for the highest vs. lowest tertiles of urine fluoride and dietary fluoride, respectively. • Associations with other fractures were less pronounced for urine fluoride, and null for dietary fluoride. • Restricting the analyses to women with consistent long-term drinking water exposures prior to baseline strengthened associations between fractures and urinary fluoride.	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• With implausible energy intakes (>3S Dab over or below the log-transformed mean) • Without data on dietary fluoride, urine for element analysis, urinary creatinine, or DXA scans on either side • With urine creatinine concentrations <0.3 or >3.0 mg/L • Not constantly drinking water fluoride from 1982 to baseline **Source of funding / support:** • Formas, the Swedish Research Council for Environment • Agricultural Sciences and Spatial Planning				

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Swedish Research Council **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified using the same method of ascertainment, recruited within the same time frame, and using the same criteria.

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, education, height, total fat mass, lean body mass, parity, smoking, physical activity, alcohol intake, prevalent diabetes at baseline, eGFR, urinary calcium or dietary calcium intake, use of calcium supplements, use of vitamin D supplements, ever use of postmenopausal hormones, ever use of corticosteroids.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (women who completed a short version of the FFQ, with incomplete FFQ data, with implausible energy intakes (>3S Dab over or below the log-transformed mean), without data on dietary fluoride, urine for element analysis, urinary creatinine, or DXA scans on either side, with urine creatinine concentrations <0.3

Risk of bias assessment			
			or >3.0 mg/L, or not constantly drinking water fluoride from 1982 to baseline)
Detection	Can we be confident in the exposure characterization?	++	"Yes, fluoride exposure levels were obtained for fluoride in food (Swedish National Food Agency, U.S. Department of Agriculture's National Fluoride Database of Selected Beverages and Foods), in tea (scientific literature), in tap water (Geological Survey of Sweden, and the Swedish Water and Wastewater Association), and urine (ion-selective electrode (Combined ISE F 800 DIN; WTW; Xylem Analytics Germany GmbH)).
	Can we be confident in the outcome assessment?	++	"Yes, the outcome was assessed for BMD (measured at the lumbar spine and femoral neck using dual energy X-ray absorptiometry [DXA; Lunar Prodigy; Lunar Corp.]) and bone fractures (using records from the National Patient Register [(NPR]). Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome (bone mineral density and bone fractures) discussed in the methods was

Risk of bias assessment			
			presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

James 2021 [29]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Before-and-after study	**Exposures:** Community water fluoridation (CWF) **Method of exposure assessment:**	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Examinations were completed at school by dental examiners and	**Statistical analysis:** • Association of interest was assessed using multivariate logistic regression • Model adjusted for the following covariates: age, gender, ownership of medical card, and	"In 2017, fluorosis prevalence was 18% in Dublin (full CWF) and 12% in Cork-Kerry (full CWF). Fluorosis was predominantly

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Ireland **Participants:** Children (7 to 9 years of age) from Dublin and Cork-Kerry in the year 2002 and 2017 **Sampling time frame:** 2002 and 2014 **Sample size (N):** <u>Year 2000</u> • Dublin = 679 • Cork-Kerry = 565 <u>Year 2017</u> • Dublin = 707	<u>Exposure group categories:</u> • Full CWF: lifetime exposure • No CWF: no exposure • Part CWF: sporadic exposure • Unknown: unknown CWF exposure **Exposure level:** CWF before and after introduction of policy measures <u>Before in 2002:</u> • 0.8 to 1.0 ppm <u>After in 2007:</u> • 0.6 to 0.8 ppm	nurses; this was performed from Jan to Jun 2002 and from Nov 2016 to May 2017 • Same methods of assessment were applied in 2007 as 2002 • Permanent teeth were assessed, and fluorosis was determined using Dean's index scores of "very mild" or higher	age of first toothpaste use **Results:** Odds (95% CI) of fluorosis prevalence in the year 2017 compared to 2002 <u>Dublin Full CWF</u> • OR = 16 (-13, 56); p = 0.312 <u>Cork-Kerry Full CWF</u> • OR = -7 (-41, 48); p = 0.771 <u>Cork-Kerry No CWF</u> • OR = 97 (-18, 373); p = 0.129	"very mild" with no statistically significant difference between 2017 and 2002." (p. 507)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Cork-Kerry = 1,148 **Sex N (%):** (2002) • Dublin Full CWF Men: 360 (53%) • Cork-Kerry Full CWF Men: 149 (45%) • Cork-Kerry No CWF Men: 103 (44%) (2017) • Dublin Full CWF Men: 324 (46%) • Cork-Kerry Full CWF Men: 178 (47%) • Cork-Kerry No CWF Men: 380 (49%) **Exclusions:**			"Among children with full CWF in Dublin, fluorosis prevalence was 18% in 2017 and 15% in 2002, and in Cork-Kerry, it was 12% in 2017 and 13% in 2002... Fluorosis prevalence among children with no CWF in Cork-Kerry was 5% in 2017 and 3% in 2002. None of the differences were statistically Significant..."	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
NR **Source of funding / support:** • Health Research Board • Department of Health and the National Oral Health Office of the Health Services Executive **Author declaration of interest:** • No COI				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***

Risk of bias assessment			
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, gender, medical card ownership, and age first used toothpaste
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (no consent to follow up, no clinical data, School refused, child moved away, fluoride status unknown, fluoride tablets/drops)

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from public water supply records
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by dental examiners assisted by dental nurses, and using Dean's Fluorosis Index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Meghe 2021 [30]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** India **Participants:** Residents with no evidence of skeletal fluorosis	**Exposures:** Fluoride levels in Ground water **Method of exposure assessment:** Data from the Groundwater Survey and Development Agency (GSDA) **Exposure level:** • ≤1mg/L	**Outcome(s):** Skeletal fluorosis **Method of outcome ascertainment:** Using physical tests designed for assessing joint pain. Classification of skeletal fluorosis was based on the clinical and radiological examinations given by Teotia, M. and Singh, K.P.	**Statistical analysis:** Descriptive analysis **Results:** **Relation of skeletal fluorosis with F- level in drinking water** • **Normal (74.8%):** ○ ≤1 ppm: 29.73% ○ 1.01–2.00: 28.14% ○ 2.01–4.00: 24.21% ○ >4.00: 17.92% • **Mild (13.2%):** ○ ≤1 ppm: 13.9% ○ 1.01–2.00: 16.47% ○ 2.01–4.00: 22.7% ○ >4.00: 46.87% • **Moderate (6.0%):** ○ ≤1 ppm: – ○ 1.01–2.00: 18.46% ○ 2.01–4.00: 25.13% ○ >4.00: 56.41%	• "Out of the total 3268 subjects 2445 subjects included in the 'normal' grade, which does not show indications of skeletal fluorosis." • "… as the concentration of fluoride increases the cases of 'normal' grade decreases."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: NR **Sample size:** 3,268 **Sex (N):** Men: 1,760 (53.86%) **Exclusions:** • Radiological evidence of skeletal fluorosis • Social reasons • Lack of availability of time	• 1.01-2.0 mg/L • 2.01-4.0 mg/L • >4.0 mg/L		• **Severe (4.1%):** ○ ≤1 ppm: – ○ 1.01–2.00: 15.55% ○ 2.01–4.00: 31.11% ○ >4.00: 53.34% • **Very severe (1.9%):** ○ ≤1 ppm: – ○ 1.01–2.00: 17.74% ○ 2.01–4.00: 25.81% ○ > 4.00: 56.45%	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: Datta Meghe Institute of Medical Sciences **Author declaration of interest:** No COI				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***

Risk of bias assessment			
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	+	Study provided some reasons for exclusion of participants (social reasons, lack of availability of time)

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from the Groundwater Survey and Development Agency (GSDA).
	Can we be confident in the outcome assessment?	–	Yes, the outcome was assessed using physical tests designed for assessing joint pain. Classification of skeletal fluorosis based on the clinical and radiological examinations given by Teotia, M. and Singh, K.P. (only for 360 out of 3268).
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome (skeletal fluorosis) discussed in the methods was presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Meng 2021 [31]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** China **Participants:** Adults (> 18 years of age) born in one of five villages (Hongguang,	**Exposures:** Fluoride levels in • Drinking water • Urine **Method of exposure assessment:** • F-ion selective electrode **Exposure level:** Fluoride quartiles in drinking water: • Q1 (≤ P25): 1.4559 mg/L • Q2 (P25 ~ P50): 1.4559 ~ 2.2434 mg/L	**Outcome(s):** • Genotoxicity (5-methylcytosine (5-mC) level) **Method of outcome ascertainment:** • Extraction and purification of genome DNA from blood: Universal cylindrical genomic DNA extraction kit • Measured 5-mC level: Methyl Flash TM Global DNA Methylation ELISA Kit	**Statistical analysis:** • Statistical significance at p </= 0.05 **Results:** Mean (SD) of 5-mC by water quartile groups in mg/L • Q1: 0.15 (0.09) • Q2: 0.11 (0.08) • Q3: 0.11 (0.08) • Q4: 0.14 (0.07) • p = 0.001 Association between fluoride and 5-mC with cubic curve fitted • R^2 = 0.061 • F = 6.045 • p = 0.001	"…fluoride could impact 5-mC level in human and rat. The U-shaped relationship was found between fluoride and 5-mC in the population and in the rats with 3 months fluoride treatments. These results clued that the disruption of DNA methylation in mammals may has a certain association with fluoride in natural exposures." (p. 5 – 6)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Xiaoshan, Fushan, Wanfa, and Leye) **Sampling time frame:** April – September 2016 **Sample size:** 281 **Sex (N):** Men: 90 (32%) **Exclusions:** NR	• Q3 (P50 ~ P75): 2.2434 ~ 3.2342 mg/L • Q4 (>P75): 3.2342 mg/L Median levels of fluoride in drinking water • 2.2434 mg/L P50 (P25, P75) levels of fluoride in water by quartile (mg/L) <u>Q1 (N = 70)</u> • 1.100 (0.767, 1.414) <u>Q2 (N = 71)</u>			

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: • National Natural Science Foundation of China • The Wu Liande Science Foundation of Harbin Medical University • Post-doctoral Scientific Research Developmental Fund of Heilongjiang Province **Author declaration of interest:**	• 1.853 (1.629, 2.069) <u>Q3 (N = 70)</u> • 2.691 (2.400, 2.949) <u>Q4 (N = 70)</u> • 4.123 (3.600, 5.200) P50 (P25, P75) levels of fluoride in urine by quartile (mg/L) <u>Q1 (N = 70)</u> • 2.040 (1.612, 3.331) <u>Q2 (N = 71)</u> • 2.432 (1.981, 3.083)			

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
No COI	<u>Q3 (N = 70)</u> • 2.432 (1.788, 3.169) <u>Q4 (N = 70)</u> • 3.780 (2.940, 5.692)			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified from the same population and recruited within the same time frame.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR

Risk of bias assessment			
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water and serum using the fluoride ion-selective electrode method
	Can we be confident in the outcome assessment?	++	Yes, the outcome (CKDu) was assessed using biopsy proven renal tubulointerstitial disease, uncontrolled hypertension or diabetes at the time of initial diagnosis, negative immunofluorescence for IgG, IgM, IgA, and C3, serum creatinine >1.2 mg/dL and/or A1M > 15.5 mg/L, HbA1C<6.5%
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Mohd Nor 2021 [32]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross sectional study	**Exposures:** Fluoride levels in public drinking water supply **Method of exposure assessment:**	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Assessment of dental fluorosis was conducted by trained clinical and calibrated examiners (NAMN).	**Statistical analysis:** • Chi-squared analyses • Logistic regression **Results:** • "Fluorosis prevalence was lower (31.9 percent) among the younger children born after the reduction of fluoride concentration in the water, compared to a prevalence of	• "Fluorosis was lower among children born after the adjustment of fluoride concentration in the water." • "Fluoridated water remained as a strong risk factor for fluorosis after downward adjustment of its

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Malaysia **Participants:** Lifelong residents aged 9- and 12-year-olds **Sampling time frame:** 2015 (calculated using the following information reported by the authors) • 9-year-old children (born	Water fluoride: State and national water quality reports **Exposure level:** • Original: 0.7 ppm • Reduced: 0.5 ppm	• Assessment of fluorosis was conducted by examining the maxillary central incisors using Dean's Fluorosis Index. • Consensus on outcome assessment must be achieved by agreement of two additional examiners, who did not participate in children's examination, with the initial examiner.	(38.4 percent) in the older cohort." **Simple logistic regression of fluorosis and infant feeding (n=830)** *Fluorosis (Deans ≥ 2),* *Type of water used to prepare formula* <u>Bottled water</u> • Fluorosis: 3 (9.4%) • No fluorosis: 29 (90.6%) • Reference <u>Tap water</u> • Fluorosis: 162 (25.7) • No fluorosis: 469 (74.3) • OR (95% CI): 3.34 (1.0–11.11) • P-value: 0.049* <u>Filtered tap water</u> • Fluorosis: 47 (28.1%)	fluoride concentration." • "Early tooth brushing practices and fluoridated toothpaste were not statistically associated with fluorosis status." "However, the prevalence of fluorosis was significantly associated with parents' education level, parents' income, fluoridated water, type of infant feeding method, age breast feeding ceased, use of

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
between 1 January and 31 December 2006 • 12-year-old children (born between 1 January and 31 December 2003) **Sample size:** 1143 children aged 9-12 years old **Sex:** Boys: 491 (43%) **Exclusions:**			• No fluorosis: 120 (71.9%) • OR (95% CI): 3.79 (1.1–13.03) • P-value: 0.035* **Simple logistic regression of fluorosis and water fluoride (n=1,143)** *Fluorosis (Deans ≥ 2),* <u>0 lifetime</u> • Fluorosis: 30 (12.30%) • No fluorosis: 517 (57.4%) • Reference <u>0.5 ppm lifetime</u> • Fluorosis: 100 (41.2%) • No fluorosis: 204 (22.7%) • OR (95% CI): 8.45 (5.45–13.10) • P-value: 0.001 <u>0.7 ppm for first 2 years and then 0.5 ppm</u> • Fluorosis: 113 (46.5%)	formula milk, duration of formula milk intake, and type of water used to reconstitute formula milk”

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Children who missed clinical examination. • Children with unerupted, partially unerupted or fractured incisor(s), or have a fixed orthodontic appliance. **Source of funding / support:** Ministry of Higher Education, Malaysia			• No fluorosis: 179 (19.9%) • OR (95% CI): 10.88 (7.03–16.84) • P-value: 0.001 **Multiple logistic regression of fluorosis (n=830)** *Fluorosis (Deans ≥ 2),* *Type of water used to prepare formula* <u>Bottled water</u> • Reference <u>Tap water</u> • OR (95% CI): 9.90 (1.28–76.38) • P-value: 0.028 <u>Filtered tap water</u> • OR (95% CI): 8.78 (1.11–69.71) 0.040 • P-value: 0.040	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI			**Multiple logistic regression of fluorosis and water fluoride (n=1,143)** <u>0 lifetime</u> • Reference <u>0.5 ppm lifetime</u> • Adjusted OR (95% CI): 5.97 (3.32–10.72) • P-value: <0.001 <u>0.7 ppm for first 2 years and then 0.5 ppm</u> • Adjusted OR (95% CI): 9.12 (5.15–16.14) • P-value: <0.001	

Risk of bias assessment		
Bias domain	***Criterion***	***Response***

Risk of bias assessment			
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected at random, during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as fluoridated toothpaste, age started toothbrushing, formula use, feeding method, parents education, and family incomes
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (children who missed clinical examination, those with unerupted, partially unerupted or fractured incisor(s), or have a fixed orthodontic appliance.)

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from state and national water quality reports
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by digital images of the maxillary incisors were taken to enable blind scoring of dental fluorosis. Images were uniquely coded to enable blind scoring. Examiners were trained on fluorosis scoring, and were blinded from the status of child's area of residence.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Rojanaworarit 2021[33]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Thailand	**Exposures** <u>Fluoride levels in</u> • Groundwater used for household water supply.	**Outcome(s):** Dental fluorosis	**Statistical analysis:** • A Wilcoxon-type test for trend to examine the trend in dental fluorosis prevalence across ordered levels of water fluoride concentration. • Poisson regression with robust standard errors to estimate dental fluorosis prevalence ratios (PR).	• "In fluoride endemic areas, groundwater containing natural fluoride utilized for household consumption resulted in high dental fluorosis prevalence, particularly in the groundwater with fluoride concentrations of ≥ 1.5 ppm." • "The finding of 23.3% prevalence with only the very mild dental fluorosis among children with time-averaged fluoride concentrations of < 0.7 ppm (the referent category) was evidence that reassured the safety of this
Participants: Children aged 6-10 years **Sampling time frame:** 2015 **Sample size:** 289	**Method of exposure assessment:** • Annual records of fluoride concentrations in the groundwater used for the household water supply corresponding to the residence of each child from 2008 to 2015 were obtained from the database at		**Results:** <u>Prevalence of dental fluorosis (%) by subdistrict</u> • Sai Ngam: 50.77 • Bang Sai Pa: 42.50 • Hin Mun: 64.18 • Bang Luang: 59.43 • Nin Phet: 9.09 <u>Prevalence of dental fluorosis (%) by water fluoride level</u> • <0.7 ppm: 23.3% • 0.7–1.49 ppm: 37.7% • ≥1.5 ppm: 64.1%	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: N (%): Boys: 153 (52.9%) **Exclusions:** Children who had not resided within the study area since birth **Source of funding / support:** Fogarty International Center of the National Institutes of Health under Award Number U2RTW010088. **Author declaration of interest:** No COI	Nakhon Pathom Provincial Public Health Office **Exposure level(s):** Time-averaged fluoride concentration (ppm) by dental fluorosis status <u>Normal (no fluorosis)</u> • Mean (SD): 2.0±1.6 • Median (IQR): 1.6 (1.1) • Range: 0.4-9.4 <u>Questionable fluorosis</u> • Mean (SD): 1.7±0.6 • Median (IQR): 1.7 (0.6) • Range: 0.6-3.0 <u>Very mild fluorosis</u>	**Method of outcome ascertainment:** • Children were examined by an "authorized dentist". • Dean's index was applied to classify the severity of dental fluorosis.	• Exact probability test; P < 0.001 <u>Severity of dental fluorosis by water fluoride level (number of cases; prevalence)</u> • <0.7 ppm: 1 (3.4%) questionable; 7 (23.3%) very mild • 0.7-1.49 ppm: 5 (8.2%) questionable; 14 (23.0%) very mild; 6 (9.8%) mild; 3 (4.9%) moderate • ≥1.5 ppm: 8 (4.1%) questionable; 96 (48.4%) very mild; 21 (10.6%) mild; 10 (5.1%) moderate <u>PR (95% CI) by time-averaged water fluoride concentrations</u> Univariable analysis • <0.7 ppm: reference • 0.7–1.49 ppm: 1.62 (0.78; 3.34); p=0.195 • ≥1.5 ppm: 2.75 (1.42; 5.31); p=0.003	recommended optimal fluoride level …" • "When the fluoride concentrations increased to the range of 0.7–1.49 ppm …, the prevalence among children in this group also increased to 37.7%, with the additional higher levels of mild and moderate severity. Although the fluoride concentrations in this range did not surpass the WHO's recommended limit of 1.5 ppm …, the results of this study were concerning as the prevalence exceeded one-

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	• Mean (SD): 2.8±2.2 • Median (IQR): 2.0 (1.4) • Range: 0.4-9.4 <u>Mild fluorosis</u> • Mean (SD): 2.8±2.3 • Median (IQR): 2.1 (1.4) • Range: 1.1-9.4 <u>Moderate fluorosis</u> • Mean (SD): 4.1±3.5 • Median (IQR): 2.0 (7.1) • Range: 1.2-9.4 <u>All</u> • Mean (SD): 2.4±2.1 • Median (IQR): 1.9 (0.9) • Range: 0.4-9.4 Time-averaged fluoride		Multivariable analysis; adjusted for child's demographic factors • <0.7 ppm: reference • 0.7–1.49 ppm: 1.62 (0.79; 3.32); p=0.190 • ≥1.5 ppm: 2.78 (1.45; 5.32); p=0.002 Multivariable analysis; adjusted for caregiver factors • <0.7 ppm: reference • 0.7–1.49 ppm: 1.61 (0.28; 9.21); p=0.592 • ≥1.5 ppm: 2.81 (0.51; 15.51); p=0.235 Multivariable analysis; adjusted for breastfeeding • <0.7 ppm: reference • 0.7–1.49 ppm: 3.08 (0.47; 20.04); p=0.238 • ≥1.5 ppm: 5.30 (0.84; 33.45); p=0.076 Multivariable analysis; adjusted for oral health behaviors	third of the children and 14.7% of the severity was beyond the very mild level." • "In the extreme group with the fluoride ≥ 1.5 ppm … the prevalence further rose to 64.1% or approximately 2.8 times the prevalence of those in the reference group. The severity beyond the very mild level also grew to 15.7%."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	concentration (ppm) by subdistrict <u>Sai Ngam</u> • Mean (SD): 3.72 (3.71) • Median (IQR): 1.40 (8.20) • Range: 0.39-9.38 <u>Bang Sai Pa</u> • Mean (SD): 3.06 (1.00) • Median (IQR): 3.35 (0.95) • Range: 1.07-3.94 <u>Hin Mun</u> • Mean (SD): 2.31 (1.20) • Median (IQR): 1.97 (0.58) • Range: 1.13-5.94 <u>Bang Luang</u> • Mean (SD): 1.76 (0.36) • Median (IQR): 1.82 (0.51) • Range: 0.84-2.20		• <0.7 ppm: reference • 0.7–1.49 ppm: 3.44 (0.48; 24.62); p=0.218 • ≥1.5 ppm: 6.46 (0.94; 44.48); p=0.058 Multivariable analysis; adjusted for all covariates • <0.7 ppm: reference • 0.7–1.49 ppm: 1.64 (0.24; 11.24); p=0.615 • ≥1.5 ppm: 2.85 (0.44; 18.52); p=0.273	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	<u>Nin Phet</u> • Mean (SD): 0.44 (0.05) • Median (IQR): 0.46 (0.10) • Range: 0.37-0.51			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	NA	Not applicable
	Was allocation to study groups adequately concealed?	NA	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants selected using same criteria. Sampling time frame reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Confounders were adjusted for.
Performance	Were experimental conditions identical across study groups?	NA	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	NA	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	None of the students declined to pariticpate
Detection	Can we be confident in the exposure characterization?	++	"annual records of fluoride concentrations in the groundwater used for the household water supply corresponding to the residence of each child from 2008 to 2015 were retrieved from the database at Nakhon Pathom Provincial Public Health Office."
	Can we be confident in the outcome assessment?	++	DF examined using Dean's Fluorosis Index
Selective reporting	Were all measured outcomes reported?	++	Outcomes discussed in the methods were reported in the results
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Sharma 2021 [34]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** India **Participants:** Children (age 6 - 19 years) residing in 12 villages from the Rudraprayag District	**Exposures:** <u>Fluoride levels in</u> • Ground water samples **Method of exposure assessment:** • Samples from 3 water sources were randomly acquired per village • Ion-selective electrode **Exposure level:** <u>Low-risk area</u> • <0.6ppm <u>Intermediate risk area</u> • 0.6 – 1.5 ppm <u>High-risk area</u>	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Determined using Deans Fluorosis Index	**Statistical analysis:** • Disease prevalence is presented as percentages by group **Results:** Positive association between drinking water fluoride levels and dental fluorosis prevalence Percent of children with dental fluorosis by drinking water fluoride levels • <0.7mg/L: 1% • > 1mg/L: 92% • p-value: <0.001	"This study confirms the positive association between the presence of fluoride-rich rocks around the water source and the prevalence of fluorosis in the population of the area." (p. 126)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: NR **Sample size:** 558 **Sex:** NR **Exclusions:** • Not “residents of selected villages in their first 8 years of life” (p. 124) • Not “eldest child … [from] each house” (p. 124)	>1.5ppm		Prevalence of dental fluorosis by geological categories (fluoride level) <u>Low-risk area (< 0.6ppm)</u> • No fluorosis <u>Intermediate risk area (0.6 – 1.5ppm)</u> • Dental fluorosis: 59.9% • Severe grade: 3.2% • Community fluorosis index: 1.05 <u>High-risk area (>1.5ppm)</u> • Dental fluorosis: 93% • Severe grade: 25.9% • Community fluorosis index: 2.59	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: Self **Author declaration of interest:** No COI				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable
	Was allocation to study groups adequately concealed?	N/A Not applicable

Risk of bias assessment			
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the ion-selective electrode (Orion company A324pH benchtop model) using the EPA-approved ISE test procedures.
	Can we be confident in the outcome assessment?	-	NR (no info on the type and/or training status of the assessors)

Risk of bias assessment			
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Silva 2021 [35]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Brazil **Participants:** 5 and 12 years old **Sampling time frame:**	**Exposures:** <u>Fluoride levels in:</u> • Drinking water (water fountains of schools/ daycares) **Method of exposure assessment:**	**Outcome(s):** • Dental fluorosis	**Statistical analysis:** • Descriptive analysis • Logistic Regression **Results:** Data for 12-year-old children [No dental fluorosis was	Adolescents consuming fluoridated water were 5 to 11 times more likely than those of consuming non-fluoridated water to develop very mild/ mild and moderate fluorosis.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
NR **Sample size:** 692 5 years old: 330 (47.6%) 12 years old: 362 (52.4%) **Sex: N (%):** Girls: 342 (49.4%) **Exclusions:** • Use of fixed orthodontic appliance • Teeth with amelogenesis imperfecta • Not being born or raised in subjected area (Teresina) or not having access to public water supply.	• Fluoride levels in drinking water: Ion Electrode Orion model No. 96-09, Orion Research Inc. coupled to Orion Star A214 Analyzer **Exposure level(s):** Fluoridated Water (FW) Conc:<0.05 µg/mL Non- Fluoridated Water (NFW) Conc: 0.5-0.6 µg/mL	**Method of outcome ascertainment:** • Thylstrup-Fejerskov index (TF)	observed in 5-year-old children in either group] • Dental Fluorosis in FW n(%)/NW n(%): Absent: 72 (40.4)/150(81.5) Very Mild/Mild: 74(41.6)/28(15.2) Moderate: 32(18.0)/6(3.3) P<0.001 Kappa index: 0.90 • Logistic regression Very mild/mild DF vs. FW (Desviance Test: p=0,088): OR:5.45 CI 95%: 3.23-9.19 P: <0.001 Moderate DF vs. FW (Desviance Test: p=0,088): OR:11.11 CI 95%: 4.43-27.87	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: • Coordination of Improvement of Higher Education Personnel (Capes) **Author declaration of interest:** No COI			P: <0.001 Reference: NFW for both Mild and moderate fluorosis Multiple analysis controlled by socioeconomic and demographics.	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected according to the same criteria and from the same eligible population. Time frame was not reported in the study.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for important confounders such as sex, socioeconomic and other demographic characteristics including mother's education, and family income.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, the study provided reasons for exclusion of participants (use of fixed orthodontic appliance, teeth with amelogenesis imperfecta, those who were not born or raised in the target area, Teresina, and those with no access to public water supply)
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water wells using a combination of ion electrode Orion (model 96-09), coupled with Orion Star analyzer (model A214)
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was done by examiners (no professional information reported), using Thylstrup-Fejerskov index (TF). Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Tkachenko 2021 [36]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Ukraine **Participants:** Children aged 7–10 years old with clinically diagnosed fluorosis from endemic fluorosis areas (exposed to drinking	**Exposures:** <u>Fluoride levels in</u> • Drinking water **Method of exposure assessment:** NR **Exposure level:** Drinking water: >1.5 ppm	**Outcome(s):** Blood level of the lipid peroxidation biomarkers (lipid acyl hydroperoxides, 2-thiobarbituric acid reactive substances (TBARS)) in the blood of children with chronic fluorosis **Method of outcome ascertainment:** • Dental fluorosis: Dean's Fluorosis Index • Blood levels: X-ray fluorescence method	**Statistical analysis:** • Kolmogorov-Smirnov test • Kruskal-Wallis test • Spearman's correlation analysis **Results:** • Children with chronic fluorosis had by 25% higher blood TBARS levels ($p < 0.05$) than the healthy subjects living in the non-fluorosis areas • There was a non-significant 17.5% increase ($p > 0.05$) in the primary products of lipid peroxidation (acyl hydroperoxides) in the blood of children from the endemic fluorosis areas, compared with the values obtained in	• "The children had higher blood TBARS levels, while the acyl hydroperoxide levels were non-significantly increased in comparison with healthy children living in the non-fluorosis area."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
water fluoride (> 1.5 ppm) for >5 years.) **Sampling time frame:** 2014 (date of the project's ethics approval) **Sample size:** 31 **Sex (N):** Boys: 15 (48.4%) **Exclusions:** • Known cardiac, lung, liver, kidney diseases or diabetes mellitus			the blood of the healthy children from the non-fluorosis area	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Use of cardiac drugs • Consumption of any vitamin or mineral supplements for at least 2 weeks before blood samples withdrawn **Source of funding / support:** NR **Author declaration of interest:** No COI				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not Applicable

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	Not Applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were identified using the same criteria and the same method of outcome ascertainment. Time frame was implied based on the approval of the respective ethics committee.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (known cardiac, lung, liver, kidney diseases or diabetes mellitus, use of cardiac drugs, or consumption of any vitamin or mineral supplements for at least 2 weeks before blood samples withdrawn)

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	+	Study used Dean's Fluorosis Index as a tool for diagnosis of dental fluorosis, which RSI considered a proxy for fluoride level exposure
	Can we be confident in the outcome assessment?	++	Yes, the blood levels of the selected elements and lipid biomarkers were measured using the X-ray fluorescence method. Dental fluorosis was assessed using Dean's Fluorosis Index. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome [blood levels of lipid peroxidation biomarkers (lipid acyl hydroperoxides, 2-thiobarbituric acid reactive substances (TBARS))] discussed in the methods was presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Wang 2021 [37]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** 6.7–13 years old school children from Tianjin, China **Sampling time frame:** 2015 **Sample size:**	**Exposure:** • Drinking *water fluoride:* 0.20–3.90 mg/L • Urinary fluoride: 0.02–5.41 mg/L • Urine creatinine: 0.30–2.99 mg/L **Method of exposure assessment:** • Fluoride concentrations in water and urine were measured by ion analyzer with a fluoride selective electrode (INESA, Shanghai, China). • Creatinine in urine (for urinary fluoride) using early morning urine samples: Creatinine	**Outcome(s):** • IQ • Dental fluorosis (DF) **Method of outcome ascertainment:** • Combined Raven's Test-The Rural in China (CRT-RC2), which is widely for cognitive ability verification test, because of less influenced by language,	**Statistical analysis:** • Descriptive analysis • Multiple linear regression models • Multiple logistic regression model • Adjustment for: age, gender, BMI, low birth weight, paternal education, maternal education, family incomes, urine creatinine (for urinary fluoride). **Results:** <u>*IQ, Linear regression*</u> • Water fluoride (mg/L): IQ scores, *β (95% CI)* ○ Q1 (≤ 0.30): Reference ○ Q2 (0.30−1.00) All: 1.77 (−0.73, 4.27) Boys: 1.40 (−2.29, 5.08) Girls: 2.51 (−1.42, 6.45) ○ Q3 (1.00−1.60) All: −2.77 (−5.44, −0.10) Boys: −4.45 (−8.41, −0.50)	• "low-to-moderate fluoride exposure was associated with the alteration of cholinergic system, DF and IQ" • "AChE partly mediated the elevated prevalence of DF and the lower probability of developing superior and above intelligence caused by fluoride."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
709 **Sex: N (%):** Girls: 328 (46.26%) **Exclusions:** NR **Source of funding / support:** • National Natural Science Foundation of China (Grants No. 82073515 and No. 81773388) • The State Key Program of National Natural Science of China (Grant No. 81430076)	determination kit (Mindray, Shenzhen, China) • Enzyme-linked immunosorbent assays (Shanghai Enzyme-linked Biotechnology, Shanghai, China) were used to detect the expression of cholinergic system.	culture, ethnic, and religion differences. • Dean's classification system for dental fluorosis	Girls: −1.72 (−5.91, 2.47) ○ Q4 (> 1.60) All: −4.10 (−6.71, −1.48) Boys: −5.74 (−9.57, −1.91) Girls: −5.27 (−9.32, −1.22) • Urinary fluoride (mg/L): IQ scores, *β (95% CI)* ○ Q1 (≤ 0.20): Reference ○ Q2 (0.20−0.48) All: −1.99 (−4.64, 0.66) Boys: −1.62 (−5.65, 2.42) Girls: −3.29 (−7.34, 0.77) ○ Q3 (0.48−0.90) All: −3.02 (−5.71, −0.33) Boys: −3.54 (−7.60, 0.52) Girls: −1.86 (−6.01, 2.29) ○ Q4 (> 0.90) All: −4.49 (−7.21, −1.77) Boys: −6.09 (−10.29, −1.90) Girls: −5.98 (−9.99, −1.96)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI	**Exposure level(s):** • Normal fluoride-exposure group: water fluoride ≤1.0 mg/L • High-fluoride-exposure group: water fluoride >1.0 mg/L		*IQ, Logistic regression* • Water fluoride (mg/L) and IQ scores [OR (95% CI)] ○ Superior and above (≥120): 0.69 (0.54, 0.90) ○ High normal (110-119): 0.86 (0.70, 1.06) ○ Normal (90-109): 1 (control) ○ Dull normal and below (≤89): 1.42 (1.08, 1.88) • Urinary fluoride (mg/L) and IQ scores [OR (95% CI)] ○ Superior and above (≥120): 0.67 (0.46, 0.97) ○ High normal (110-119): 0.90 (0.68, 1.18) ○ Normal (90-109): 1 (control) ○ Dull normal and below (≤89): 1.39 (0.97, 2.00) • AChE (nmol/L) and IQ scores [OR (95% CI)] ○ Q1 (≤0.30): Reference ○ Q2 (0.30−1.00) Superior and above (≥ 120): 1.67 (0.92, 3.02) High normal (110-119): 1.22 (0.73, 2.04)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Normal (90-109): 1 (control) Dull normal and below (≤ 89): 0.96 (0.40, 2.27) ○ Q3 (1.00−1.60) Superior and above (≥ 120): 0.47 (0.24, 0.94) High normal (110-119): 0.78 (0.47, 1.30) Normal (90-109): 1 (control) Dull normal and below (≤ 89): 0.63 (0.27, 1.47) ○ Q4 (>1.60) Superior and above (≥ 120): 0.54 (0.29, 1.00) High normal (110-119): 0.92 (0.53, 1.57) Normal (90-109): 1 (control) Dull normal and below (≤ 89): 1.68 (0.77, 3.64)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			DF, Prevalence • Water fluoride (mg/L): dental fluorosis, PR *(95% CI)* ○ Q1 (≤ 0.30): Reference ○ Q2 (0.30−1.00) Crude: 1.21 (0.86, 1.70) Adjusted: 1.20 (0.85, 1.69) ○ Q3 (1.00−1.60) Crude: 3.78 (2.90, 4.94) Adjusted: 3.79 (2.90, 4.95) ○ Q4 (>1.60) Crude: 3.90 (3.00, 5.08) Adjusted: 3.97 (3.04, 5.17) • Urinary fluoride (mg/L): dental fluorosis, PR *(95% CI)* ○ Q1 (≤0.20): Reference ○ Q2 (0.20−0.48) Crude: 1.42 (1.09, 1.86) Adjusted: 1.66 (1.28, 2.14) ○ Q3 (0.48−0.90) Crude: 2.18 (1.72, 2.75) Adjusted: 2.73 (2.17, 3.44) ○ Q4 (>0.90)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Crude: 2.56 (2.04, 3.21) Adjusted: 3.24 (2.58, 4.07) • Cholinergic system AChE (nmol/L) and DF/IQ [PR (95% CI)] *Either DF or IQ <120* ○ Q1 (≤ 133.66): Reference ○ Q2 (133.66–157.97) Crude: 1.09 (0.94,1.26) Adjusted: 1.06 (0.92,1.22) ○ Q3 (157.97–184.03): Crude: 1.14 (1.00,1.31) Adjusted: 1.12 (0.97,1.28) ○ Q4 (>184.03) Crude: 1.21 (1.06,1.38) Adjusted: 1.22 (1.07,1.38) *DF and IQ <120* ○ Q1 (≤ 133.66): Reference ○ Q2 (133.66–157.97) Crude: 1.29 (1.08,1.54)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Adjusted: 1.27 (1.07,1.50) ○ Q3 (157.97–184.03): Crude: 1.37 (1.16,1.62) Adjusted: 1.37 (1.17,1.62) ○ Q4 (>184.03) Crude: 1.46 (1.25,1.72) Adjusted: 1.44 (1.23,1.68) • "Sensitivity analyses were conducted for the association between fluoride exposure, DF, IQ, and cholinergic system by adjusting for the covariates among demographics, development, socioeconomics, and delivery conditions. We obtained similar results to what we found in the present analyses."	

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe, according to the same criteria and from the same eligible population.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it was adjusted for major confounders such as age, sex, BMI, low birth weight, paternal education, maternal education, family incomes, and urine creatinine (for urinary fluoride).
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reported data was complete with no attrition or exclusion from analysis.
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from drinking water samples that were collected from the local source of water supply in each village. Fluoride concentrations in water and urine were measured by ion analyzer with a fluoride selective electrode (INESA, Shanghai, China).

Risk of bias assessment					
Bias domain	***Criterion***	***Response***			
	Can we be confident in the outcome assessment?	++	Yes, IQ was consistently assessed by trained teachers who were blinded to the children's exposure status using the Combined Raven's Test-The Rural in China (CRT-RC2), which is widely for cognitive ability verification test, because of less influenced by language, culture, ethnic, and religion differences.	++	DF was independently assessed by two trained dentists who were blinded to the children's exposure status independently The diagnosis of DF was estimated by Dean's fluorosis index.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Yani 2021 [38]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Indonesia **Participants:** 6–12 years old students from two different areas with different levels of drinking water fluoride in Palu City, with no history of head trauma, chronic	**Exposure:** • Ground water **Method of exposure assessment:** • NR	**Outcome(s):** • IQ • Dental fluorosis	**Statistical analysis:** • Univariate analysis • Bivariate analysis **Results:** Dental fluorosis • High-fluoride area: ○ Total: 37 (61.7%) ○ Questionable (score 1): 1 (0%) ○ Very mild (score 2): 10 (0%) ○ Mild (score 3): 11 (11%) ○ Moderate (score 4): 8 (8%) ○ Severe (score 5): 7 (7%)	• "There is a relationship between Fluoride level in well water and the incidence of fluorosis in students, where the incidence of fluorosis was higher in the high fluorine area than in the low fluorine area." • "The intelligence of children who suffered from fluorosis is lower than the intelligence of children who do not suffer from fluorosis." • "The level of intelligence of students who live

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**

disease, or were not undergoing treatment.
 	
Sampling time frame:
 	
NR
 	
Sample size:
 	
100
 	
Sex: N (%):
 	
Females: 64 (64.0%)
 	
Exclusions:
 	
• NR
Source of funding / support:
 	
• NR
Author declaration of interest:
 	
• No COI
	Exposure level(s):
	
	• High fluoride area: 1.6 ppm
	• Low fluoride area: 0.10 ppm
		Method of outcome ascertainment:
		
		• Dental fluorosis was assessed using Dean's fluorosis index
		• IQ was assessed using Raven's Color Progressive Matrix component.
			• Low-fluoride area:
			  ○ Total: 3 (7.5%)
			  ○ Questionable (score 1): 2 (%)
			  ○ Very mild (score 2): 1 (1%)
			  ○ Mild (score 3): 0 (0%)
			  ○ Moderate (score 4): 0 (0%)
			  ○ Severe (score 5): 0 (0%)
			
			IQ
			
			• High-fluoride area:
			  ○ Low: 17 (28.3%)
			  ○ High: 43 (71.7%)
			• Low-fluoride area:
			  ○ Low: 0 (0%)
			  ○ High: 40 (100%)
			
			IQ and Dental fluorosis
			
			• Dental fluorosis:
			  ○ Low: 15 (37.5%)
			  ○ High: 25 (62.5%)
			• No dental fluorosis:
				in the high-fluorine area is lower than students who live in low fluorine area."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			○ Low: 2 (3.3%) ○ High: 28 (96.6%)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected according to the same criteria and from the same eligible population. However, the timeframe was not reported.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reported data was complete with no attrition or exclusion from analysis.
Detection	Can we be confident in the exposure characterization?	–	NR

Risk of bias assessment					
Bias domain	***Criterion***	***Response***			
	Can we be confident in the outcome assessment?	+	Yes, IQ was consistently assessed by a trained philology using the Raven's Coloured Progressive Matrices. No information reported on assessor blindness	+	Yes, DF was consistently assessed by a trained dentist using Dean's fluorosis index. No information reported on assessor blindness
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Yu 2021 [39]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** School children aged 7 to 13 years old **Sampling time frame:** 2015 **Sample size:** 952 **Sex: N (%):**	• Exposure: Fluoride content in • Drinking water • Urine • Hair and nail **Method of exposure assessment:** • Water samples were collected from each public supply in the villages. • Fluoride concentration was assessed using the national standardized ion-selective electrode method in China	Outcome(s): • IQ	**Statistical analysis:** • LASSO Binomial regression • Linear regression model • The Adaptive Rank Truncated Product (ARTP) for investigating the associations of intelligence with genetic variations at the gene or pathway level. **Results:** • Water fluoride (mg/L) ○ High (IQ ≥ 120): 0.70 (0.40–1.00) ○ Non-high (70 ≤ IQ<120): 1.00 (0.50–1.90) • Urinary fluoride (mg/L) ○ High (IQ ≥ 120): 0.33 (0.13–0.81) ○ Non-high (70 ≤ IQ <120): 0.60 (0.16–2.22) • Hair fluoride (μg/g)	• "Our study suggests that fluoride is inversely associated with intelligence." • "The interactions of fluoride with mitochondrial function-related SNP-set, genes and pathways may also be involved in high intelligence loss."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Girls: 481 (50.5%) **Exclusions:** • Non-respondents • Congenital or acquired diseases affecting intelligence. • Neurologic disorders • Refused to provide blood, hair or nail samples • Low genotypic detection rate • Hair permed or dyed, or with hair samples less than 0.2 g (n = 250). Nails dyed or with nails samples less than 0.2 g (n = 340).	• An early-morning spot urine sample was collected from each subject. • Hair samples were collected from the occipital zone of the scalp.		○ High (IQ ≥ 120): 8.26 (5.72–10.48) ○ Non-high (70 ≤ IQ <120): 14.39 (10.25–20.56) • Nail fluoride (μg/g) ○ High (IQ ≥ 120): 11.71 (8.53–14.64) ○ Non-high (70 ≤ IQ <120): 19.76 (14.16–27.32) <u>Fluoride exposure and high intelligence: OR (95% CI)</u> • Water fluoride (mg/L) ○ Tertile 1 (≤0.60) Reference ○ Tertile 2 (0.61–1.40)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: • The State Key Program of National Natural Science Foundation of China (Grant No. 81430076). • The National Program for Support of Top-notch Young Professionals and Health commission of Hubei Province **Author declaration of interest:** No COI	**Exposure level(s):** • Water fluoride (mg/L) ○ Tertile 1 (≤0.60) ○ Tertile 2 (0.61–1.40) ○ Tertile 3 (>1.40) • Urinary fluoride (mg/L) ○ Tertile 1 (≤0.22) ○ Tertile 2 (0.23–1.80) ○ Tertile 3 (>1.80) • Hair fluoride (μg/g) ○ Tertile 1 (≤10.40) ○ Tertile 2 (10.41–17.02) ○ Tertile 3 (>17.02) • Nail fluoride (μg/g) ○ Tertile 1 (≤14.64) ○ Tertile 2 (14.65–23.41) ○ Tertile 3 (>23.41)	**Method of outcome ascertainment:** • IQ scores were measured by the second edition of Combined Raven's Test – The Rural in China (CRT-RC2) for children aged 7 to 13 years.	Crude: 0.95 (0.65, 1.38) Adjusted: 0.94 (0.64, 1.37) ○ Tertile 3 (>1.40) Crude: 0.38 (0.24, 0.59) Adjusted: 0.39 (0.25, 0.61) • Urinary fluoride (mg/L) ○ Tertile 1 (≤0.22) Reference ○ Tertile 2 (0.23–1.80) Crude: 1.26 (0.87, 1.83) Adjusted: 1.26 (0.87, 1.84) ○ Tertile 3 (>1.80) Crude: 0.41 (0.26, 0.65)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Adjusted: 0.41 (0.26, 0.66) • Hair fluoride (µg/g) ○ Tertile 1 (≤10.40) Reference ○ Tertile 2 (10.41–17.02) Crude: 0.16 (0.10, 0.29) Adjusted: 0.16 (0.09, 0.29) ○ Tertile 3 (>17.02) Crude: 0.08 (0.04, 0.16) Adjusted: 0.08 (0.04, 0.16) • Nail fluoride (µg/g) ○ Tertile 1 (≤14.64) Reference ○ Tertile 2 (14.65–23.41) Crude: 0.15 (0.08, 0.29)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Adjusted: 0.15 (0.08, 0.29) ○ Tertile 3 (>23.41) Crude: 0.09 (0.04, 0.18) Adjusted: 0.09 (0.04, 0.19) <u>Does-response relationships of IQ scores with fluoride exposures</u> • *β and 95% CI for every 0.50 mg/L increment of water fluoride or urinary fluoride* • *β and 95% CI for every 1.00 µg/g increment of hair fluoride or nail fluoride.* • *Adjustment: age, sex, maternal education and paternal education.* • Water fluoride (mg/L)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			○ 0.20-3.40 Crude: -1.24 (-1.48, -0.99) Adjusted: -1.16 (-1.41, -0.91) ○ 3.40-3.90 Crude: -5.36 (-8.54, -2.18) Adjusted: -4.21 (-7.54, -0.87) • Urinary fluoride (mg/L) ○ 0.01-1.60 Crude: 0.96 (0.29, 1.63) Adjusted: 1.01 (0.34, 1.68) ○ 1.60-2.50 Crude: -5.08 (-6.94, -3.22)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Adjusted: -5.23 (-7.07, -3.39) ○ 2.50-5.54 Crude: -0.50 (-1.13, 0.14) Adjusted: -0.34 (-0.98, 0.30) • Hair fluoride (µg/g) ○ 3.23-10.50 Crude: -2.34 (-2.69, -1.99) Adjusted: -2.34 (-2.69, -1.99) ○ 10.50-45.04 Crude: -0.41 (-0.49, -0.34) Adjusted: -0.42 (-0.50, -0.34) • Nail fluoride (µg/g) ○ 2.08-14.50	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Crude: -1.11 (-1.41, -0.81) Adjusted: -1.10 (-1.41, -0.80) ○ 14.50-99.60 Crude: -0.50 (-0.56, -0.44) Adjusted: -0.49 (-0.55, -0.43) <u>Interaction of SNP-set score with fluoride exposure on high intelligence OR (95% CI).</u> • *The P-value for interaction (p-inter) was adjusted for age, sex, maternal education and paternal education.* • *High SNP: -set score group (-1.59 to 0.00):* • *Low SNP-set score group (-2.90 to -1.59):*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Water fluoride (binary variable based on the limit of 1.00 mg/L) ○ Sample size: 952 ○ High SNP: 0.33 (0.20, 0.55) ○ Low SNP: 0.27 (0.14, 0.54) ○ p-inter: 0.030 • Urinary fluoride (binary variable based on the limit of 1.60 mg/L) ○ Sample size: 952 ○ High SNP: 0.37 (0.22, 0.62) ○ Low SNP: 0.32 (0.16, 0.63) ○ p-inter: 0.040 • Hair fluoride (binary variable based on the median level of 14.00 µg/g) ○ Sample size: 719 ○ High SNP: 0.17 (0.08, 0.34)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			○ Low SNP: 0.12 (0.04, 0.35) ○ p-inter: 0.010 • Nail fluoride (binary variable based on the median level of 19.60 µg/g) ○ Sample size: 638 ○ High SNP: 0.13 (0.06, 0.31) ○ Low SNP: 0.12 (0.04, 0.37) ○ p-inter: 0.242	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe, according to the same criteria and from the same eligible population.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it was adjusted for major confounders such as age, sex, maternal education and paternal education

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (non-respondents, congenital or acquired diseases affecting intelligence, neurologic disorders, those who refused to provide blood, hair or nail samples, low genotypic detection rate, permed or dyed hair, or with hair samples less than 0.2 g (n = 250), and dyed nails or with nails samples less than 0.2 g (n = 340).). There were no significant differences between those included compared to those excluded in both “high” and “non-high” intelligence groups in most characteristics, except for parental education and family income, where the numbers excluded were appreciably higher than those included. Similarly those excluded were more likely to have experienced maternal drinking, smoking or anemia during pregnancy, or encountered a problematic delivery.
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from drinking water samples that were collected from the local source of water supply in each village. Fluoride concentration in water

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
			was assessed using the national standardized ion-selective electrode method in China.
	Can we be confident in the outcome assessment?	+	Yes, IQ was consistently assessed by professionals (no credentials reported) who supervised the children during the assessment. IQ scores were measured using the second edition of Combined Raven's Test – The Rural in China (CRT-RC2) for children aged 7 to 13 years. No information reported on assessor blindness
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Zhao 2021 [40]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** children, aged 6–11 years old, from endemic and non-endemic fluorosis areas in Tianjin, China. **Sampling time frame:**	**Exposure:** Fluoride concentration in • Drinking water • Urine **Method of exposure assessment:** • Urinary fluoride: The national standardized method ion analyzer EA940 with F-ion selective electrode (Shanghai constant magnetic	**Outcome(s):** • IQ	**Statistical analysis:** • Multivariable linear regression models (associations between fluoride and IQ scores) • Multiplicative and additive models (appraising single gene-environment interaction) • Generalized multifactor dimensionality reduction, GMDR (evaluating high-dimensional interactions of gene-gene and gene-environment).	• "Dopamine relative genes may modify the association between fluoride and intelligence, and a potential interaction among fluoride exposure and DA relative genes on IQ." • "fluoride exposure is inversely related to children's IQ; DA related genes polymorphism (ANKK1 Taq1A, COMT rs4680, DAT1 40 bp VNTR and MAOA uVNTR) have modifying effects of fluoride exposure on IQ; UF, ANKK1

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
2018 **Sample size:** 567 **Sex: N (%):** Girls: 283 (49.9%) **Exclusions:** • Negative long-term residence • Mental retardation in an immediate family member • Missing IQ test, questionnaire or physical examination • No results of genotyping measurement **Source of funding / support:** The National Natural Science Foundation of	electronic technology Co, Ltd, China) **Exposure level(s):** Fluoride in drinking water: • High fluoride areas: 1.53–2.84 mg/L • Non-endemic fluorosis area (WF: 0.15–0.37 mg/L Fluoride in urine: • Urinary fluoride concentration was not normally distributed, with a median (quantile 1, quantile 3) of 1.03 (0.72, 1.47) mg/L	**Method of outcome ascertainment:** The Combined Raven's Test (modified in China)	**Results:** <u>Associations between UF and IQ scores</u> • Overall: Log_UF were inversely linear associated with IQ score (P < 0.05) in both crude model and adjusted model • β (95% CI): ○ Crude: - 5.159 (- 8.996, - 1.321) ○ Adjusted: - 5.957 (- 9.712, - 2.202) ○ Bootstrapped estimation of the variance: (95% CI: - 10.356, - 1.834; p=0.006)	Taq1A, COMT Val 158 Met and MAOA uVNTR have a high-dimensional interaction on IQ."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
China (Grant No. 81573107, 81372934). **Author declaration of interest:** No COI	• After log transformation, the mean (±SD) Log_UF was 0.015 (±0.252)			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe, according to the same criteria and from the same eligible population.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it was adjusted for major confounders such age, gender, BMI, paternal education level, maternal education level, household income, abnormal birth and maternal age at delivery.

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (negative long-term residence, mental retardation in an immediate family member, missing IQ test, questionnaire or physical examination, or no results of genotyping measurement).
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride concentration in water was assessed using the national standardized method ion analyzer EA940 with F-ion selective electrode (Shanghai constant magnetic electronic technology Co, Ltd, China) .
	Can we be confident in the outcome assessment?	++	Outcome was consistently assessed using The Combined Raven's Test (modified in China). Test administrators were blinded to participants' drinking water fluoride exposure levels. All participant assessments were conducted by trained professionals and under the supervision of qualified teachers, and public health and medical doctors.
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction.

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Bai 2020 [41]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** USA	**Exposures:** Fluoride levels in • Drinking water • Serum **Method of exposure assessment:** Levels of fluoride in water and serum were tested using the ion-	**Outcome(s):** Sex steroid hormones [testosterone, estradiol and sex hormone-binding globulin (SHBG)] **Method of outcome ascertainment:**	**Statistical analysis:** • Analysis of variance and Chi-square test for continuous and categorical variables, respectively. • Adjusted linear regression (age, gender, race, family PIR, serum cotinine, BMI category, seasonal period when surveyed and session of blood sample collection)	"The data indicated gender- and age-specific inverse associations of fluoride in plasma and water with sex steroid hormones of total testosterone, estradiol and

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: US children and adolescents 6–19 years old (NHANES survey) **Sampling time frame:** 2013 – 2016 **Sample size:** 3,392 **Sex (N):** Males Total: 780 (50.6%) Children: 936 (50.6%)	specific electrode method **Exposure level:** • **Water fluoride (mg/L)** ○ Total: 0.36 (0.30, 0.42) ○ Male children: 0.40 (0.32, 0.47) ○ Male adolescents: 0.34 (0.28, 0.40) ○ Female children: 0.37 (0.29, 0.44) ○ Female adolescents: 0.35 (0.28, 0.41) ○ p-value: 0.143 • **Plasma fluoride (umol/L)** ○ Total: 0.35 (0.33, 0.37) ○ Male children: 0.38 (0.36, 0.41) ○ Male adolescents: 0.34 (0.32, 0.36)	• Total testosterone and estradiol: isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) • SHBG: reaction of SHBG with immuno-antibodies and chemo-luminescence measurements of the reaction products	**Results:** • Compared with subjects at the first tertile of plasma fluoride, percent changes (95% CI) in testosterone were: ○ Second tertile: –8.08% (–17.36%, 2.25%) ○ Third tertile: –21.65% (–30.44%, –11.75%) ○ P trend <0.001 • Male adolescents at the third tertile of plasma fluoride had decreased levels of testosterone: –21.09% (–36.61% to –1.77%). • Similar inverse associations were also found when investigating the relationships between plasma fluoride and estradiol. • Decreased levels of SHBG associated with	SHBG in U.S. children and adolescents.”

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Adolescents: 1,716 (50.6%) **Exclusions:** Participants missing information on fluoride levels in plasma or water, sex steroid hormones of testosterone, estradiol, SHBG, or the examined covariates. **Source of funding / support:** National Natural	○ Female children: 0.36 (0.34, 0.37) ○ Female adolescents: 0.33 (0.31, 0.35) ○ p-value: <0.001		water and plasma fluoride ○ Male adolescents (third tertile): –9.39% (–17.25% to –0.78%) ○ Female children (second tertile): –10.78% (–17.55% to –3.45%) **Percent change in testosterone (95% CI) at tertiles T2 and T3, compared to T1:** <u>Total</u> • T2: -7.95 (-20.47, 6.56) • T3: -8.11 (-15.84, 0.33) • p trend = 0.069 <u>Male Children</u> • T2: 10.90 (-8.11, 33.85) • T3: -7.56 (-21.80, 9.27) • p trend = 0.458 <u>Male Adolescents</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Science Foundation of China **Author declaration of interest:** No COI			• T2: -2.35 (-19.83, 18.94) • T3: -7.43 (-24.79, 13.94) • p trend = 0.461 <u>Female Children</u> • T2: -1.07 (-14.11, 13.96) • T3: -3.97 (-15.95, 9.72) • p trend = 0.549 <u>Female Adolescents</u> • T2: -2.08 (-11.75, 8.66) • T3: -3.58 (-14.75, 9.06) • p = trend 0.540 **Percent change in Estradiol (95% CI) at tertiles T2 and T3, compared to T1:** <u>Total</u> • T2: -4.55 (-16.08, 8.56) • T3: 1.48 (-6.97, 10.70) • p trend = 0.896	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			<u>Male Children</u> • T2: 2.08 (-2.97, 7.39) • T3: 0.72 (-4.07, 5.75) • p trend = 0.705 <u>Male Adolescents</u> • T2: -4.56 (-19.04, 12.52) • T3: -1.25 (-14.54, 14.10) • p trend = 0.823 <u>Female Children</u> • T2: -15.59 (-32.04, 4.84) • T3: -7.25 (-22.74, 11.35) • p trend = 0.337 <u>Female Adolescents</u> • T2: 3.50 (-21.43, 36.33) • T3: 9.49 (-13.47, 38.53) • p trend = 0.457 **Percent change in SHBG (95% CI) at**	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			tertiles T2 and T3, compared to T1: <u>Total</u> • T2: 2.71 (-4.84, 10.86) • T3: -2.75 (-9.69, 4.74) • p = trend 0.557 <u>Male Children</u> • T2: 5.38 (-2.14, 13.48) • T3: -4.14 (-10.65, 2.85) • p trend = 0.322 <u>Male Adolescents</u> • T2: 0.38 (-7.95, 9.47) • T3: -9.39 (-17.25, -0.78) • p trend = 0.038 <u>Female Children</u> • T2: -1.74 (-11.50, 9.10) • T3: 0.12 (-7.47, 8.34) • p trend = 0.984 <u>Female Adolescents</u> • T2: 2.09 (-13.3, 19.98) • T3: -0.37 (-12.06, 12.88)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• p trend = 0.996	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified using the same method of ascertainment, recruited within the same time frame, and using the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, gender, race, family PIR, serum cotinine, BMI category, seasonal period when surveyed and session of blood sample collection
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (participants missing information on fluoride levels in plasma or water, sex steroid hormones of testosterone, estradiol, SHBG, or the examined covariates.)
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels in water and serum were measured using the ion-specific electrode method
	Can we be confident in the outcome assessment?	++	Yes, the outcome was assessed for Total testosterone and estradiol using the isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS); and for SHBG using the reaction of SHBG with immuno-antibodies and chemo-luminescence measurements of the reaction products. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.

Risk of bias assessment			
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome (steroid sex hormones) discussed in the methods was presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Cui Y 2020 [42]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:**	**Exposures:** Fluoride levels in • Urine	**Outcome(s):** • IQ scores • Thyroid Stimulating Hormone (TSH) • Dopamine (DA)	**Statistical analysis:** • Descriptive statistics **Results:**	Although fluoride was not the main focus[xxvii], the study reported non-significant

[xxvii] RSI conclusion provided as the author's reported conclusion did not include information on effects caused by exposure to fluoride

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Cross-sectional study **Country:** China **Participants:** School aged children (7 – 12 years) from Tianjin **Sampling time frame:** 2014 - 2018 **Sample size:** 498	**Method of exposure assessment:** • Fluoride ion selective electrode method **Exposure level:** Distribution by urinary fluoride levels (N; %) <u>< 1.6 mg/L</u> • N = 396 (79.52) <u>1.6 – 2.5 mg/L</u> • N = 66 (13.25) <u>≥ 2.5 mg/L</u> • N = 36 (7.23)	**Method of outcome ascertainment:** • IQ: Combined Raven's Test (CRT) • TSH: measured in serum using electrochemical luminescence method • DA: measured in plasma using ELISA and DA kit	Mean (±SD) IQ by urinary fluoride levels <u>< 1.6 mg/L</u> • 112.16 (±11.50) <u>1.6 – 2.5 mg/L</u> • 112.05 (±12.01) <u>≥ 2.5 mg/L</u> • 110.00 (±14.92) <u>p-value</u> • 0.578 Median (q1-q3) TSH in uIU/mL by urinary fluoride levels <u>< 1.6 mg/L</u> • 2.81 (2.21 – 3.81) <u>1.6 – 2.5 mg/L</u>	frequency differences between urinary fluoride levels and IQ scores, and TSH and DA levels

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: Boys: 248 (49.8%) **Exclusions:** • Had incomplete information • Insufficient samples of blood **Source of funding / support:** • National Nature Science Foundation of China • Tianjin Health Inspection Fund **Author declaration of interest:**			• 2.82 (2.01 – 3.82) <u>≥ 2.5 mg/L</u> • 3.29 (2.30 – 4.48) <u>p-value</u> • 0.287 Median (q1-q3) DA in ng/L by urinary fluoride levels <u>< 1.6 mg/L</u> • 5.62 (3.08 – 12.15) <u>1.6 – 2.5 mg/L</u> • 5.77 (3.01 – 12.59) <u>≥ 2.5 mg/L</u> • 7.24 (2.16 – 15.23) <u>p-value</u> 0.925	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified from the same population and recruited within the same time frame.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment							
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable				
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants such as insufficient blood samples or incomplete data				
Detection	Can we be confident in the exposure characterization?	++	Exposure was measured in urine using fluoride ion selective electrode method (Chinese standard WS/T 89-2015).				
	Can we be confident in the outcome assessment?	+	IQ measured using Combined Raven's Test (CRT). Unclear blinding	++	TSH measured in serum using electrochemical luminescence method	++	DA measured in plasma using ELISA and DA kit
Selective reporting	Were all measured outcomes reported?	++	Yes, all primary outcomes (IQ, thyroid hormones and dopamine) discussed in methods were presented in results section with adequate level of detail for data extraction				

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Das 2020 [43]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study	**Exposures:** <u>Fluoride levels in</u> • Water wells • Filtration plants • Commercial brand water bottles	**Outcome(s):** Dental Fluorosis **Method of outcome ascertainment:** • Assessments were completed by two	**Statistical analysis:** NR **Results:**	"The results revealed that fluoride levels varied between 0.03 and 3.8 ppm. People who drank well water

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Saudi Arabia **Participants:** Dental college patients (aged 9 to 50 years) **Sampling time frame:** July – December 2019 **Sample size:** 1,150 **Sex N:** Men: 609 (53%)	**Method of exposure assessment:** • Collected samples (N= 63) from 12 regions/cities and 9 water bottle brands **Exposure level:** Mean (SD) Fluoride levels in ppm by water source type • Well Water 1.97 (0.20) • Filtered Water 1.05 (0.69) • Bottled Water 1.09 (0.10)	dentists and two dental assistants • Severity was determined using Dean's index	Association between dental fluorosis and sources of drinking water <u>Well Water</u> • None: 163 • Questionable: 141 • Very Mild: 105 • Mild: 71 • Moderate: 12 • Severe: 3 • Total: 495 <u>Filtered Water</u> • None: 414 • Questionable: 197 • Very Mild: 36 • Mild: 5 • Moderate: 3 • Severe: 0 • Total: 665 <u>Total</u> • None: 577 • Questionable: 338 • Very Mild: 141	displayed increased fluoride levels (>0.81 ppm). The prevalence of dental fluorosis was established to be 20.43% among the total number of examined patients. The findings of this study show very mild to moderate dental fluorosis prevail among the patients who consume well water in the Asir region."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: Patients without primary or permanent teeth fully erupted **Source of funding / support:** Deanship of Scientific Research **Author declaration of interest:** No COI			• Mild: 76 • Moderate: 15 • Severe: 3 • Total: 1150 <u>p-value</u> • <0.002	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the ion chromatography system (ExStik® FL700 Fluoride Meter, USA).
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was done by 2 dentists and 2 dental assistants, using Dean's fluorosis index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Fernandes 2020 [44]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** Brazil **Participants:** Children (6 to 12 years of age) from rural public schools in São João do Rio do Peixe, Poço José	**Exposures:** Fluoride level in • Water samples **Method of exposure assessment:** "Combined ion-specific fluoride electrode … and a reference electrode … connected to an ion analyser 710 A" (p. 476) **Exposure level:** Level of residual fluoride in water (ppm)**:**	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Single examiner with notetaker determined dental fluorosis using the Thysltrup and Fejerskov criteria	**Statistical analysis:** NR **Results:** N (%) dental fluorosis absent • ≤0.7 ppm F: 306 (63.1) • >0.7 ppm F: 69 (55.2) N (%) dental fluorosis present • ≤0.7 ppm F: 179 (36.9%) • >0.7 ppm F: 56 (44.8%)	"The prevalence of dental fluorosis in group II [>0.7 ppm F] was higher (44.8%), but it was not significantly different from group I [<0.7 ppm F] (36.9%)." (p. 477)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
de Moura, Marizópolis, and Uiraúna **Sampling time frame:** NR **Sample size:** 610 **Sex N (%):** Men: 329 (53.9%) **Exclusions:** • Use fixed orthodontic appliance • Have reading difficulties	Range: 0.06 – 1.98			

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Have tooth malformations **Source of funding / support:** NR **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable

Risk of bias assessment			
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (using fixed orthodontic appliance, have reading difficulties, or have tooth malformations)
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the combined ion specific fluoride electrode (ORION—9409BN) and a reference electrode (900200) connected to an ion analyser 710 A (ORION).
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by a single examiner with notetaker using the Thysltrup and

Risk of bias assessment			
			Fejerskov criteria. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Godebo 2020 [45]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:**	**Exposures** Fluoride levels in • Drinking water • Urine	**Outcome:** Skeletal fluorosis	**Statistical analysis:** • Bivariate and multivariable linear regression analyses • adjusted for age, sex, BMI, smoking, current tooth paste use	• Negative associations between F- exposure and bone quality at all three bone sites • Fluoride-induced deterioration of bone

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Cross-sectional **Country:** Ethiopia **Participants:** Adolescents and adult farmers living in the MER rural area **Sampling time frame:** 2018-2019 **Study population:** 341 **Sex:** (men): 55.1%	**Exposure assessment:** 24-hour urinary F-content was determined using the ion selective electrode and the hexamethyldisiloxane (HMDS)-facilitated diffusion method (Rango et al. 2017). <u>Water F-concentrations:</u> <u>Mean (SD)</u> • *Water intake (liter/day): 1.3 ± 0.63* • *Fl in groundwater (mg/L): 6.8 ±4.30*	**Method of outcome ascertainment:** • Bone scan in multiple skeletal sites, using a novel mobile non-ionizing ultrasound device. Results were examined using the same assessment criteria • X-ray validation for a subset of participation, where radiographs were analyzed by a radiologist/co-author with a specialization in skeletal fluorosis	**Results:** • 1 mg/L increase in F- in drinking water was related to reduction of 15.8 m/s (95% CI: −21.3 to −10.3) of adult tibial SOS. • 1 mg/L increase in 24-h urinary F- (range: 0.04–39.5 mg/L) was linked to a reduction of 8.4 m/s (95% CI: −12.7, −4.12) of adult tibial SOS. • Adolescents: weaker and non-significant inverse associations between F-exposure and SOS Age, gender, and BMI were more significant predictors than in adults	quality in humans, likely reflecting a combination of factors related to SOS: net bone loss, abnormal mineralization and collagen formation, or altered microarchitecture.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: individuals who were judged as incapable of undergoing detailed health examinations. **Source of funding/ support:** National Institute of Environmental Health Sciences **Author declaration of interest:** Not reported	• *Fl intake (mg/day): 9.13 ± 7.30* <u>Urinary F-concentrations:</u> <u>Mean (SD)</u> *F- in 24-h urine (mg/L):* 8.2 ± 7.6 *F- excretion (mg):* 5.01 ± 4.5			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were enrolled during 2 sampling periods (between 2018 and 2019), from 25 rural communities in the Main Ethiopian Rift (MER), each of which were primarily dependent on a single groundwater well.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes (age, sex, BMI, smoking, current toothpaste use)
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Not considered a risk of bias as there were few eligible participants who got excluded based on a judgment

Risk of bias assessment			
			that they would be incapable of undergoing detailed health examinations.
Detection	Can we be confident in the exposure characterization?	++	Yes, 24-hour urinary F- content was determined for all groups, within the same time-frame, and using the same tool: ion selective electrode and the hexamethyldisiloxane (HMDS)-facilitated diffusion method
	Can we be confident in the outcome assessment?	++	Yes, all participants underwent the same bone scan on the same 3 skeletal sites for adults, and 2 sites for children, using a standard “novel” mobile non-ionizing ultrasound device. Results were examined using the same. Validation using X-ray radiographs was completed for a subset of participants by a radiologist/co-author with a specialization in skeletal fluorosis
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Kim 2020 [46]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Case-control **Country:**	**Exposures:** Fluoride levels in • Water **Method of exposure assessment:** NR	**Outcome(s):** Osteosarcoma (bone cancer) **Method of outcome ascertainment:** • Phase 1: histological confirmation of diagnosis followed by phone interviews	**Statistical analysis:** • Conditional logistic regression to assess the association of community water fluoridation with osteosarcoma. **Results:**	"Findings from this study demonstrated that community water fluoridation is not associated with an increased risk for osteosarcoma."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
USA **Participants:** Phase 1 • Cases: all patients younger than 40 years old, who were diagnosed with osteosarcoma • Controls: patients with other bone tumors or non-neoplastic conditions, identified during the same periods, and from the same orthopedic surgery department as cases. • Controls were matched to cases on sex, age ±5 years, and distance from the hospital **Sampling time frame:**	**Exposure level:** Lived in a fluoridated area (0.7 ppm) • No ○ Cases: 58 (24.6%) ○ Controls: 81 (19.8%) ○ *Reference* • Yes ○ Cases: 178 (75.4%) ○ Controls: 328 (80.2%) *OR: 0.76, 95% CI: (0.52 to 1.11), p-value: 0.156*	• Phase 2: pathology reports	• A modestly significant interaction existed between fluoridation living status and bottled water use (P = 0.047). • Risk of osteosarcoma (adjusted): ○ For ever having lived in a fluoridated area for nonbottled water drinkers: [OR= 0.51 (95% CI: 0.31 - 0.84) P = 0.008)]. ○ For bottled water drinkers: [OR=1.86 (95% CI: 0.54 - 6.41; P = 0.326).	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Phase 1: 1989–1993 • Phase 2: 1994–2000 **Sample size:** • Phase 1: cases (209), controls (440) • Phase 2: cases (108), controls (296) **Sex (N):** Phase 1 & 2 combined: • Cases: men: 142 (60.2%) • Controls: men 248 (60.6%) **Exclusions:** Phase 1				

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Patients older than 40 years of age at diagnosis • Prior radiotherapy • Renal dialysis Phase 2 • Radiotherapy • Renal dialysis • Foreign nationals who were in the United States solely for treatment **Source of funding / support:** • Statistical analysis: CDI Research, Inc. • Phase 1: the National Institute of Environmental Health Sciences (NIH). • Data collection: the New England Research Institute.				

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Phase 2 was funded by the National Cancer Institute (NIH) and the National Institute of Dental and Craniofacial Research (NIH). **Author declaration of interest:** Declaration of interest provided				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Cases and controls were recruited from the same population, within the same time frame timeframe, and with the same eligibility criteria other than by outcome of interest
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, race, ethnicity, income, ever lived in urban residence, distance from hospital, and ever drank bottled water (included only when bottled water * fluoridation exposure interaction was not significant), family income (via zip code and Census data)
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable

Risk of bias assessment			
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (age >40, radiotherapy, renal dialysis, missing residential history, non matching cases or controls)
Detection	Can we be confident in the exposure characterization?	+	Yes, fluoride exposure levels were obtained from state dental directors, state level administrators and from the 1992 CDC Fluoridation Census if needed.
	Can we be confident in the outcome assessment?	++	Yes, the outcome was assessed in cases and controls using medical records and histopathology reports. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome discussed in methods was presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Krishna 2020 [47]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Case-control study **Country:** India **Participants:** Patients (45 – 75 years of age) from RL Jalappa Hospital and Research Center	**Exposures:** <u>Fluoride levels in</u> • Serum **Method of exposure assessment:** ISE Thermo Scientific Orion-5 Instrument **Exposure level:** Mean (SD) levels of fluoride in ppm by study groups <u>Controls</u> • 0.0949 (0.12) <u>T2DM without CKD</u>	**Outcome(s):** Diabetes Mellitus and Diabetic nephropathy using serum renal parameters **Method of outcome ascertainment:** "…Vitros 5.1 FS dry chemistry auto analyzer from Ortho Clinical Diagnostics (OCD) United States, based on the principle of "reflectance photometry".	**Statistical analysis:** • Analysis conducted using one way Analysis of Variance test • Statistical significance at $p<0.05$ **Results:** Pearson correlation between serum fluoride and parameters (N = 30). <u>Fasting Blood Sugar</u> • 0.28 <u>Postprandial Blood Sugar</u> • 0.44* <u>Urea</u> • 0.107 <u>Serum Creatinine</u>	• "Our results showed that Fasting, post prandial blood glucose values and serum Fluoride were significantly higher in T2DM without CKD group as compared to the controls and T2DM with CKD." (p. 571) • "This study also supports the hypothesis of increase serum Fluoride increases DM and DN which is evident from the results." (p. 575)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: July 2019 – September 2019 **Sample size:** 90 **Sex:** NR **Exclusions:** • Non Kolar resident, with diabetes mellitus (DM), and no fluoride exposure • Use of drugs • Use of other factors that can result in diabetes or diabetic nephropathy	• 0.6318 (0.59) T2DM with CKD • 0.5128 (0.30) p-value 0.001		• 0.08 Albumin • 0.102 Sodium • 0.005 Potassium • 0.101	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Going through dialysis • Has acute kidney injury • Has hepatobiliary disorder that result in proteinuria or albuminuria • Has gestational DM, type 1 DM, or monogenic diabetic syndrome **Source of funding / support:** NR **Author declaration of interest:** NR				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified from the same population and recruited within the same time frame.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Yes, it accounted for some confounders as age and sex
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, the study provided reasons for exclusion of participants (non-residents, with diabetes mellitus (DM), and no fluoride exposure, use of drugs, use of other factors that can result in diabetes or diabetic nephropathy, dialysis, acute kidney injury,

Risk of bias assessment			
			hepatobiliary disorder resulting in proteinuria or albuminuria, gestational DM, DM type I, or monogenic diabetic syndrome)
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride in serum was measured in serum using the ISE Thermo Scientific Orion-5 Instrument
	Can we be confident in the outcome assessment?	++	Yes, the outcome (DM serum/renal parameters) was measured using Vitros 5.1 FS dry chemistry auto analyzer from Ortho Clinical Diagnostics (OCD) United States, based on the principle of reflectance photometry
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Lee 2020 [48]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Ecological study **Country:** South Korea **Participants:** All residents in the Cheongju region	**Exposures:** Fluoride levels in • Water **Method of exposure assessment:** Data from the Korean Microdata Integrated Service (MIDS) of Statistics Korea. **Exposure level:** NR	**Outcome(s):** • Hip fracture • Osteoporosis • Bone cancer **Method of outcome ascertainment:** Data from the National Health Insurance Service (NHIS) for select ICD-10 codes.	**Statistical analysis:** • Standardized incidence ratios to estimate the disease risk. • Hierarchical Bayesian Poisson spatio-temporal regression model to investigate the association between select bone diseases and CWF considering space and time interaction **Results:** • The posterior relative risks (RR): ○ Hip fracture: RR: 0.95, 95% CI: 0.87- 1.05 ○ Os≥≥teoporosis	"These findings suggest that CWF is not associated with adverse health risks related to bone diseases."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: 1 January 2004 - 31 December 2013 **Sample size:** • Fluoridated areas: 4,406,021 • Non-fluoridated areas: 2,270,959 **Sex (N):** • Fluoridated areas: Men: 2,200,104 (49.9%) • Non-fluoridated areas: Men: 1,126,495 (49.6%)			RR: 0.94, 95% CI: 0.87-1.02 ○ <u>Bone cancer</u> RR: 1.20, 95% CI: 0.89-1.61 (a little high due to smaller sample size compared to the other bone diseases) The RR of the selected bone diseases increased over time but did not increase in the CWF area compared to non-CWF areas.	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: Reported no exclusions due to use of customized data from the NHIS **Source of funding / support:** Division of Oral Health Policy, Ministry of Health and Welfare, Republic of Korea **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were identified using the same method of ascertainment, recruited within the same time frame, and using the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Study accounted only for age and sex
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable

Risk of bias assessment			
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study reported no missing information on any of the study participants due to extraction of customized data from the Korean NHIS.
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from the Microdata Integrated Service (MIDS) of Statistics Korea.
	Can we be confident in the outcome assessment?	++	Yes, the outcome was assessed using the respective ICD-10 codes from the National Health Insurance Service (NHIS) records. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome discussed in methods was presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Nanayakkara 2020 [49]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Sri Lanka **Participants:** Men with chronic kidney disease of uncertain aetiology (CKDu) and healthy controls	**Exposures:** <u>Fluoride levels in</u> • Serum • Water **Method of exposure assessment:** • Drinking water samples from Girandurukotte and Medawachchiya • Blood samples from males with CKDu and healthy controls • Samples analyzed using fluoride ion-selective electrode **Exposure level:**	**Outcome(s):** CKDu **Method of outcome ascertainment:** • Diagnosed CKDu ("biopsy proven renal tubulointerstitial disease, uncontrolled hypertension or diabetes at the time of initial diagnosis, negative immunofluorescence for IgG, IgM, IgA, and C3, serum creatinine >1.2 mg/dL and/or A1M > 15.5 mg/L, HbA1C<6.5%") • Healthy controls ("no history of hypertension, diabetes	**Statistical analysis:** • Analysis conducted using the analysis of variance (ANOVA) test • Statistical significance at $p \leq 0.05$ **Results:** Mean serum fluoride level (SD) by CKDu stage <u>Stage 0 (N = 276)</u> • 35.5 µg/L (16.3) <u>Stage 1 (N = 10)</u> • 38.1 µg/L (18.1) <u>Stage 2 (N = 60)</u> • 53.9 µg/L (34.2)*	• "CKDu patients showed significantly higher serum fluoride concentrations than the healthy controls." • "The estimated glomerular filtration level was inversely proportional to the serum fluoride concentration, indicating the accumulation of fluoride in the body with the progression of CKDu, which can further aggravate renal tissue damage." (p. 4)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: NR **Sample size (N):** • Men with CKDu = 311 • Healthy Controls = 276 **Sex:** NR **Exclusions:** NR **Source of funding / support:**	*Mean (SD) levels of fluoride in drinking water* • 0.68 mg/L (0.48) *Mean (SD) levels of fluoride in serum by stages of CKD* <u>Stage 0 (N = 276)</u> • 35.5 µg/L (16.3) <u>Stage 1 (N = 10)</u> • 38.1 (18.1) <u>Stage 2 (N = 60)</u> • 53.9 (34.2)	or renal impairment, blood pressure not more than 140/90 mmHg, no proteinuria or glycosuria based on the dipstick urine test, HbA1C<6.5%, serum creatinine <1.2 mg/dL and/ or A1M < 15.5 mg/L")	<u>Stage 3 (N = 160)</u> • 82.8 µg/L (41.9)* <u>Stage 4 (N = 72)</u> • 123.4 µg/L (59.9)* <u>Stage 5 (N = 9)</u> • 123.9 µg/L (52.6)* * p<0.05 compared to controls	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology **Author declaration of interest:** No COI				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Exposure measured in water and serum using the fluoride ion-selective electrode method
	Can we be confident in the outcome assessment?	++	Yes, the outcome (CKDu) was assessed using biopsy proven renal tubulointerstitial disease, uncontrolled hypertension or diabetes at the time of initial

Risk of bias assessment			
			diagnosis, negative immunofluorescence for IgG, IgM, IgA, and C3, serum creatinine >1.2 mg/dL and/or A1M > 15.5 mg/L, HbA1C<6.5%
Selective reporting	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Russ 2020 [50]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:**	**Exposures:** Aluminum and fluoride levels in drinking water	**Outcome:** Dementia **Method of outcome ascertainment:**	**Statistical analysis:** • Cox proportional hazards models for the association between aluminium and fluoride levels in drinking water	• "Higher levels of aluminium and fluoride were related to dementia risk in a population of men and women who

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Cohort study **Country:** Scotland **Participants:** all people born in 1921 and at school in Scotland in June 1932 who took part in a comprehensive national intelligence test at a mean age of 11 years (Scottish Mental Survey 1932) **Sampling time frame:** 2005-2014	**Method of exposure assessment:** Data from the Drinking Water Quality Regulator for Scotland (DWQR) **Fluoride in drinking water:** • Mean: 53.4 µg/L ±16.0 • Range: 23.8–181.1	Any mention of *ICD-9 codes* 290.0–290.4, 290.8, 290.9, 291.1, 291.2, 294.1, 294.2, 294.8, 294.9, and 331.0–331.912 and *ICD-10 codes:* F00-F05.1, F09, G30, and G3113 recorded on electronic medical records or death certificates after 2004, or from primary care records, specifically the Greater Glasgow & Clyde Nursing Homes Medical Practice, which exclusively treated	with dementia in men and women separately • Age in years over the age of 84 years was the timescale • All models were additionally adjusted for IQ at age 11 years • Sensitivity analysis was conducted, adjusting for SIMD rank. • Additional model for the interaction between aluminium and fluoride. **Results:** Out of an analytic sample of 2728 men and 4262 women alive in 2005:	consumed relatively low drinking-water levels of both." • No statistical interaction between aluminium and fluoride levels in relation to dementia. • A dose-response pattern was observed between mean fluoride levels and dementia in women [HR: 1.34 (95% CI: 1.28–1.41, P <0.001)] and men [HR: 1.30 (95% CI: 1.22–1.39), P <0.001], with dementia risk more than doubled in the

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size (N): Initial: 37,597 Analysis: 6,980 **Sex: N (%)** Men: Initial: 19,272 (51%) Analysis: 2,728 (39%) **Exclusions:** Participants missing residential location, died before the monitoring period began in 2005, or		residents of nursing homes	• 622 men and 1350 women developed dementia. • All participants were approximately 84 years old at start of the exposure period • Follow-up duration: ○ *Mean: 2.7 years* ○ *SD: 2.1 years* ○ *Range: 0–7 years* • Fluoride ○ Mean: 53.4 µg/L ○ *SD: 16.0* ○ *Range: 23.8–181.1*	highest quartile compared with the lowest.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
missing childhood IQ test results **Source of funding/ support:** Alzheimer Scotland through the Marjorie MacBeath bequest **Author declaration of interest:** None				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***

Risk of bias assessment			
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	++	Yes, using the same inclusion/exclusion criteria, and using the same methods for ascertainment of exposure and outcome, identified participants included all people born in 1921 and at school in Scotland in June 1932 who took part in a comprehensive national intelligence test at a mean age of 11 years (Scottish Mental Survey 1932).
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Yes, Cox proportional hazards models was used to assess the association between fluoride (and aluminum) levels in drinking water with dementia in men and women separately, adjusting for childhood IQ and SIMD. Given the narrow age cohort (all born in 1921) reflected a homogenous sample with no major factors to confound the findings.

Risk of bias assessment			
			No information could be identified regarding participants' exposure to drinking water before 2005, i.e., for the first 84 years of their lives.
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	**++**	Study provided reasons for exclusion of participants (missing residential location, died before the monitoring period began in 2005, or missing childhood IQ test results), which were not related to the outcome
Detection	Can we be confident in the exposure characterization?	**++**	Yes, data on levels of fluoride exposure were consistently drawn within the same timeframe, from the same source: Drinking Water Quality Regulator for Scotland (DWQR). Sampling sites were identified by longitude and latitude and were widely distributed across

Risk of bias assessment			
			Scotland, particularly where the population is more concentrated
	Can we be confident in the outcome assessment?	++	Yes, outcome was determined using relevant ICD9/10 codes for dementia, as recorded in on electronic medical records or death certificates after 2004, or from primary care records, specifically the Greater Glasgow & Clyde Nursing Homes Medical Practice, which exclusively treated residents of nursing homes
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome (dementia) discussed in methods were presented in results section with adequate level of detail
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Stangvaltaite-Mouhat 2020 [51]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** cross-sectional (part of the Lithuanian National Oral Health Survey) **Country:** Lithuania **Participants:** Adults between 35 and 74 years old **Sampling time frame:** NR	**Exposures:** Fluoride levels in drinking water **Method of exposure assessment:** Fluoride levels in drinking water were provided by the water suppliers. **Exposure level:** • ≤ 1 ppm • > 1 ppm	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Assessments were conducted by one trained and calibrated examiner, assisted by a dental assistant. • DF was assessed using the WHO index [World Health Organization, 2013]	**Statistical analysis:** • Prevalence for each age group was calculated using descriptive statistics (chi-square test, likelihood ratio, and the independent-sample t-test). • Analytical methods for DF were not reported **Results:** **Dental fluorosis prevalence by age group and gender** <u>35–44 years</u> *Males* • Yes: 5 (4%) • No: 125 (96%)	"Signs of fluorosis were detected in 2% of participants (N=21) and the presence of fluorosis did not associate significantly with higher levels of fluoride in the drinking water (data not shown)."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size: 1,397 **Sex:** Men 462 (33.1%) **Exclusions:** NR **Source of funding / support:** The Borrow Foundation **Author declaration of interest:** No COI			*Females* • Yes: 8 (4%) • No: 215 (96%) <u>45–54 years</u> *Males* • Yes: 2 (2%) • No: 102 (98%) *Females* • Yes: 3 (1%) • No: 204 (99%) <u>55–64 years</u> *Males* • Yes: 1 (1%) • No: 111 (99%) *Females* • Yes: 0 (0%) • No: 248 (100%) <u>65-74 years</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Males • Yes: 2 (2%) • No: 114 (98%) *Females* • Yes: 0 (0%) • No: 253 (100%) **Dental fluorosis prevalence by water fluoride level** ***≤ 1 ppm*** <u>35–44 years</u> • Males: 121 (93%) • Females: 198 (88%) <u>45–54 years</u> • Males: 95 (91%) • Females: 181 (87%) <u>55–64 years</u> • Males: 100 (89%)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Females: 201 (80%) <u>65-74 years</u> • Males: 96 (83%) • Females: 204 (80%) ***>1ppm*** <u>35–44 years</u> • Males: 9 (7%) • Females: 26 (12%) <u>45–54 years</u> • Males: 9 (9%) • Females: 26 (13%) <u>55–64 years</u> • Males: 12 (11%) • Females: 49 (20%) <u>65-74 years</u> • Males: 20 (17%) • Females: 50 (20%)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from public water suppliers
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was done by one trained and calibrated examiner, and a dental assistant, using the WHO index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Sun 2020 [52]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** Female farmers (20 – 60 years of age) from 6 villages (3 endemic fluorosis villages with fluoride levels > 1.0 mg/L; 3 control villages	**Exposures:** Fluoride levels in • Urine **Method of exposure assessment:** Fluoride ion-selective electrode **Exposure level:** NR	**Outcome(s):** • Reduction of bone mineral density (BMD) via CALCA gene methylation **Method of outcome ascertainment:** • BMD: Standalone ultrasound bone densitometer • CALCA methylation: Quantitative methylation-specific polymerases chain reaction	**Statistical analysis:** • Statistical significance at $p<0.05$ • Associations of fluoride with CALCA exon 1 methylation levels and T-scores stratified by age groups were adjusted for age, menopause, BMI, high-density lipoprotein-cholesterol (HDL-C) and alkaline phosphatase (ALP) **Results:** Adjusted association of fluoride with CALCA exon 1 methylation levels • $r = 0.022$ • $p = 0.576$	"…decreased BMD in women may be associated with exposure to excessive fluoride in an age-specific manner, which may be modified by methylation of CALCA exon 1."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
with fluoride levels < 1.0 mg/L) in Tongxu County **Sampling time frame:** NR **Sample size:** 722 **Sex (%):** Women: 100% **Exclusions:** • Had "history of chronic bone disease, bone fracture, cognitive impairment, chronic kidney disease"			Adjusted association (β; 95% CI) of fluoride (mg/L) with CALCA exon 1 methylation levels by age groups 20 – 60 yrs (N = 722) • 0.270 (-0.621, 1.162) 20 – 39 yrs (N = 135) • 1.656 (-1.464, 4.776) 40 – 44 yrs (N = 70) • 4.953 (1.162, 8.743) 45 – 49 yrs (N = 139) • -0.152 (-2.673, 2.369) 50 – 54 yrs (N = 220) • 0.405 (-0.797, 1.607) 55 – 60 yrs (N = 158) • -1.643 (-3.657, 0.370)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Were using bisphosphonates • Had incomplete data **Source of funding / support:** • National Natural Science Foundation of China • Scientific and Technological Project of Henan Province **Author declaration of interest:** No COI			Correlation between fluoride and T-score • r = 0.019 • p = 0.611 Adjusted association (β; 95% CI) of fluoride (mg/L) with T-score by age groups <u>20 – 60 yrs</u> (N = 722) • 0.010 (-0.032, 0.051) <u>20 – 39 yrs</u> (N = 135) • 0.001 (-0.139, 0.139) <u>40 – 44 yrs</u> (N = 70) • 0.106 (-0.021, 0.233) <u>45 – 49 yrs</u> (N = 139) • 0.095 (-0.022, 0.212)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			50 – 54 yrs (N = 220) • -0.063 (-0.129, -0.002) 55 – 60 yrs (N = 158) • 0.035 (-0.044, 0.114) Interaction between fluoride and CALCA exon 1 methylation on BMD was assessed • "…found evidence of a significant association, as manifested by increased BMD in women aged 45-49 years induced by the interactive effect of the highest methylation of CALCA exon 1 (tertile 3) and fluoride exposure (β = 5.338, P = 0.016)"	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, menopause, BMI, high-density lipoprotein-cholesterol (HDL-C) and alkaline phosphatase (ALP)
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (history of chronic bone disease, bone fracture, cognitive impairment, chronic kidney disease, use of bisphosphonates, or incomplete data)
Detection	Can we be confident in the exposure characterization?	++	Yes, the urinary levels of fluoride was measured by a fluoride ion-selective
	Can we be confident in the outcome assessment?	++	Yes, the outcome BMD was assessed using a standalone ultrasound bone densitometer. CALCA methylation was assessed using quantitative methylation-specific polymerases chain reaction method.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome (BMD reduction) discussed in methods were presented in results section with adequate level of detail
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were	++	None identified

Risk of bias assessment			
	appropriate and researchers adhered to the study protocol)?		

Till 2020 [53]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cohort study **Country:** Canada **Participants:** English-/French-speaking women, >17 years old, and less than 14 weeks gestation were recruited	**Exposures:** Fluoride levels in • Drinking water • Urine samples (maternal) **Method of exposure assessment:** • Water fluoride concentrations recorded in municipal water reports. • Maternal urinary fluoride (MUF) adjusted for specific gravity as a proxy of fetal fluoride exposure.	**Outcomes:** Intellectual function **Method of outcome ascertainment:** • IQ scores were measured by the Wechsler Primary and Preschool Scale of Intelligence-III at 3–4 years using United States population-based normative data (mean=100, SD=15). • Outcomes included Full Scale IQ, Verbal	**Statistical analysis:** • Linear regression for the association between fluoride and IQ scores • Impact of feeding status (breast-fed versus formula-fed) and fetal fluoride exposure on the association • Adjusted for child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and quality of the child's home environment **Results:**	"Exposure to increasing levels of fluoride in tap water was associated with diminished non-verbal intellectual abilities; the effect was more pronounced among formula-fed children.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
from prenatal clinics in 10 North American cities (Maternal-Infant Research on Environmental Chemicals program) **Sampling time frame:** 2008-2011 **Sample size (N):** 398 mother-child pairs (67.3% of those who completed testing) reported drinking tap water, had water fluoride data and complete covariate data (BF: n=200; FF: n=198)	**Water Fluoride concentration (mg/L)** *Breastfed≥6 mo.* • Fluoridated: 0.58 (0.08) • Non- Fluoridated: 0.13 (0.06) *Formula-fed* • Fluoridated: 0.59 (0.07) • Non- Fluoridated: 0.13 (0.05) P-value: 0.18 **Infant fluoride intake (mg/day)** *Breastfed≥6 mo.* • Fluoridated:	IQ, and Performance IQ (PIQ)	• Thirty-eight percent of mother-child dyads lived in fluoridated communities. • An increase of 0.5 mg/L in water fluoride concentration *(almost equal to the difference between fluoridated and non-fluoridated regions)* corresponded to reduction in performance IQ: ○ *Formula-fed:* *9.3-point (95% CI: −13.77, −4.76)* ○ *Breastfed:* *6.2-point (95% CI: −10.45, −1.94).* • Association remained significant upon controlling for fetal fluoride exposure	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: Children: girls *Breastfed, fl: 51%* *Breastfed, non-fl: 53%* *Formula, fl: 54%* *Formula, non-fl: 47%* **Exclusions:** Participants with known fetal abnormality, had any medical complications, or known illicit drug use during pregnancy. **Source of funding/ support:** • National Institute of Environmental Health Science (NIEHS) • Health Canada	0.12 (0.07) • Non- Fluoridated: 0.02 (0.02) <u>*Formula-fed*</u> • Non- Fluoridated: 0.34 (0.12) • Non- Fluoridated: 0.08 (0.04) P-value: <.001		○ <u>*Formula-fed:*</u> *(B=−7.93, 95% CI: −12.84, −3.01)* ○ <u>*Breastfed:*</u> *(B=−6.30, 95% CI: −10.92, −1.68)*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Ontario Ministry of the Environment, • CIHR **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	**++**	Yes, mothers were selected using the same criteria, during the same timeframe, from the same cities, with similar race, mean age at delivery, and employment.

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, analysis was adjusted for child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and quality of the child's home environment
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Of all children who completed IQ testing, 398 pairs (67.3%) reported drinking tap water, had water fluoride data and complete covariate data (breastfed=200; formula-fed: n=198) Characteristics of women included in the analysis (398) were not substantially different from the original cohort (N=1945) or the subset without complete water fluoride and covariate data (n=203)

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	+	Yes, data on levels of fluoride exposure were consistently drawn within the same timeframe, from the same source: municipal water reports. Maternal urinary fluoride (MUF) adjusted for specific gravity (non-validated) was used as a proxy of fetal fluoride exposure
	Can we be confident in the outcome assessment?	++	Yes, IQ scores were measured by the Wechsler Primary and Preschool Scale of Intelligence-III at 3–4 years using United States population-based normative data (mean=100, SD=15).
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcome discussed in methods was presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	+	Possibility of recall or response bias of mothers completing the questionnaire

Wang 2020 [54]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** Resident children, aged 7–13 years, randomly selected from endemic and non-endemic	**Exposures:** Fluoride levels in • Drinking water • Urine samples **Method of exposure assessment:** • Water samples were collected randomly from the public water supplies in each village • Urine samples for every child were collected in the early morning before breakfast. • Fluoride levels in water and urine were measured using an ion	**Outcomes:** • Thyroid hormone dysfunction (TT3, TT4, FT3, FT4 and TSH levels in serum) • Intelligence (IQ) **Method of outcome ascertainment:** • Chemiluminescent microparticle immunoassay on the ARCHITECT i4000SR was employed to quantify thyroid hormone levels in serum.	**Statistical analysis:** • Multi-variable linear and logistical regression models for the associations among fluoride exposure, thyroid function and IQ scores • Sensitivity analyses were conducted by modifying covariates adjusted in multivariable models: age, sex, BMI, maternal education, paternal education, household income, low birth weight **Results:** (Mean ± SD)	"low-moderate fluoride exposure is associated with alterations in childhood thyroid function that may modify the association between fluoride and intelligence"

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**

fluorosis areas in Tianjin, China.
 	
Sampling time frame:
2015
 	
Sample size (N):
571
 	
Sex:
Boys: 292 (51.1%)
 	
Exclusions:
• Not long- term residents of the area
• Had congenital or acquired diseases affecting intelligence,
• History of cerebral trauma and neurological disorders
• Positive screening test (e.g. hepatitis B,
	analyzer EA940 with a fluoride ion selective electrode (Wu et al., 2015).
	
	Water fluoride level:
	Mean (mg/L): 1.39
	±1.01
		• A Combined Raven's Test for Rural China (CRT-RC2) was taken to evaluate the IQ of each child	<u>Fluoride</u>
			• Water fluoride (mg/L)
			  ○ *1.39 ± 1.01*
			• Urinary fluoride (mg/L)
			  ○ *1.28 ± 1.30*
			
			<u>Thyroid hormones:</u>
			• TT3 (ng/mL):
			  ○ *1.32 ± 0.19*
			• FT3 (pg/mL):
			  ○ *3.28 ± 0.32*
			• TT4 (µg/dL):
			  ○ *6.86 ± 1.16*
			• FT4 (ng/dL):
			  ○ *1.13 ± 0.12*
			• TSH (uIU/mL):
			  ○ *2.57 ± 1.29*
			
			• Every 1 mg/L increment of water fluoride was associated with
			  ○ *0.006 ng/mL increase in TT3*
			  ○ *0.013 pg/mL increase in FT3*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Treponema palladium, Down's syndrome) • Exposure to smoking and drinking during maternal pregnancy **Source of funding/ support:** • State Key Program of National Natural Science of China • National Natural Science Foundation of China • Fundamental Research Funds for the Central Universities **Author declaration of interest:** No COI			○ *0.083 ng/mL decrease in TT4* ○ *0.01 ng/mL decrease in FT4* ○ *0.13 μIU/mL increase in TSH* • Every 1 mg/L increment of urinary fluoride was associated with ○ *0.007 ng/mL increase in TT3* ○ *0.02 pg/mL increase in FT3* ○ *0.09 ng/mL decrease in TT4* ○ *0.009 ng/mL decrease in FT4* ○ *0.11 μIU/mL increase in TSH* • Fluoride exposure was inversely related to IQ scores ○ *Water fluoride: B=−1.59 (95% CI: −2.61, −0.57)* ○ *Urinary fluoride:*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			B=−1.21 (95% CI: −1.99, −0.44). • Higher TT3, FT3 were related to the increased odds of children having high normal intelligence ○ *TT3 OR=3.41 (95% CI: 1.04, 11.12)* ○ *FT3 OR=3.277 (95% CI: 1.62, 6.62)* • A significant modification effect by TSH on the association between urinary fluoride and IQ scores, without mediation by thyroid hormones	

Risk of bias assessment			
Bias domain	***Criterion***	***Outcome 1: Thyroid dysfunction***	***Outcome 2: IQ***
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	**++**	Yes, children were selected using the same criteria, during the same timeframe, from villages that were similar in population and general demographics, and assessed for exposure and outcome using the same methods
Confounding	Did the study design or analysis account for important confounding and modifying variables?	**++**	Yes, the analysis was adjusted for age, sex, BMI, maternal education, paternal education, household income, low birth weight
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	

Risk of bias assessment					
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	There was no loss of participants due to attrition		
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride levels in water and urine were within the same timeframe and using the same method: ion analyzer EA940 with a fluoride ion selective electrode (Shanghai constant magnetic electronic technology Co, Ltd, China), and in accordance with the national standardized method in China (Wu et al., 2015).		
	Can we be confident in the outcome assessment?	++	Yes, thyroid hormone levels in serum were assessed for all children using the same method: Chemiluminescent microparticle immunoassay on the ARCHITECT i4000SR	++	Yes, a Combined Raven's Test for Rural China (CRT-RC2) was taken to evaluate the IQ of each child
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction		

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

An 2019 [55]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China (Henan Pr)	**Exposures:** Fluoride levels in • Community • Urine **Method of exposure assessment:**	**Outcomes:** Levels of reproductive hormones (SHBG and ABP) in serum **Method of outcome ascertainment:** An enzyme-linked immunosorbent assay	**Statistical analysis:** • Independent sample t-tests, one-way ANOVA and multivariate linear regression analyses • A generalized linear model was used to calculate gene-environment and gene-gene effects. • The genotypic distribution of ESRα among control subjects accorded with the	chronic fluoride exposure from drinking water is associated with alterations of serum SHBG and ABP concentrations in local male farmers and that the effect of fluoride exposure on

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: • 18-55 male farmers who were born or lived for at least 5 years before marriage in one of the 7 villages (Henan Province) • Four villages with endemic fluorosis and three control villages, based on water fluoride concentration in relation to the standard of national drinking water quality (1.0 mg L−1 GB5749-2006). **Sampling time frame:** 2011-2012	a fluoride ion-selective electrode (Shanghai Exactitude, Shanghai, China) assay was used to measure urine fluoride levels.	(R&D systems, Minneapolis, USA) was used to measure serum concentrations of SHBG and ABP.	Hardy-Weinberg equilibrium (P=0.193, PvuII; P=0.050, XbaI; P=0.410, rs3798577). • Analysis adjusted for age, diet, exercise habits, tobacco use, alcohol and tea consumption **Results:** <u>Water fluoride (Mean ± SD)</u> • Group of villages with high exposure (HEG): *2.44±1.88 mg/L* • Group of villages with low exposure (LEG): *0.37± 0.15 mg/L*	ABP levels vary depending on ESRα gene polymorphisms

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size (N): 348 **Sex:** Males (100%) **Exclusions:** Participants who resided in other places for at least 1 year, had a history of chronic bone disease, underwent bisphosphonate, hormonal or calcitonin therapy, or suffered from colds over the two			<u>Urinary fluoride (Mean ± SD)</u> • Fluoride (mg/L) ○ *HEG 2.66 ± 1.03* ○ *LEG 0.95 ± 0.31* *P-value: <0.001* <u>Reproductive hormones (Mean ± SD)</u> • ABP (nmol/L) ○ *HEG 19.86 ± 22.46* ○ *LEG 24.04 ± 26.94* *P-value= 0.144* • SHBG (nmol/L) ○ *HEG 30.07 ± 28.32* ○ *LEG 35.90 ± 28.58* *P-value= 0.012*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
weeks prior to study initiation **Source of funding/ support:** • National Natural Science Foundation of China • Henan Department of Science and Technology, China **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	**++**	• Yes, farmers were selected using the same inclusion/exclusion criteria, cluster sampling method, ascertainment methods, within the same timeframe from 7 villages in Henan Province, China. • Participants were comparable between the high exposure group (4 villages with endemic fluorosis), and low exposure group (3 control villages), based on water fluoride concentration in relation to the standard of national drinking water quality (1.0 mg L−1 GB5749-2006). • Overall participation rate was 96.94%.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	**+**	• Analyses were adjusted for age, urinary fluoride level, diet, exercise habits, tobacco use, alcohol and tea consumption

Risk of bias assessment			
			• Other indicators reflective of male reproductive function, including sexual life quality or adverse newborn birth outcomes were not accounted for due to small sample size.
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	**++**	Overall non-participation rate was less than 4% and is unlikely to have biased the results of the analyses.
Detection	Can we be confident in the exposure characterization?	**++**	Yes, fluoride levels in urine were measured for all participants using the same fluoride ion-selective electrode (Shanghai Exactitude, Shanghai, China)
	Can we be confident in the outcome assessment?	**++**	Yes, levels of reproductive hormones (SHBG and ABP) in serum were measured for all participants using an enzyme-linked immunosorbent assay (R&D systems, Minneapolis, USA)

Risk of bias assessment			
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Crnosija 2019 [56]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Ecological study	**Exposures:** Fluoride levels in drinking water **Method of exposure assessment:**	**Outcomes:** Secondary bone cancer **Method of outcome ascertainment:**	**Statistical analysis:** • Ordinary least squares regression and diagnostic tests to determine the necessity of a spatial regression using GeoDa 1.8.16.4, and queen firstorder	We found no evidence of an association between community water fluoridation category and

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: USA (NY State) **Participants:** +18 years old inpatients with metastatic bone cancer who were admitted to a New York State hospital for receiving care **Sampling time frame:** January 1, 2008 – December 31, 2010	Data from the water quality reports from individual providers in the different NY State counties	Data on inpatient cancer patients admitted with an ICD9 code for secondary bone cancer (198.5) to a New York State hospital for relevant care, which was extracted from the Statewide Planning and Research Cooperative System (SPARCS) database; an inpatient/outpatient record of all hospital admissions collected and curated by New York State's	contiguity for generating spatial weights. • Series of regression models with county-level percentage of secondary bone cancer as the dependent variable **Results:** <u>Fluoride in drinking water:</u> • 0.7 mg/L (45 counties) • 0.8 mg/L (2 counties) • 0.5 mg/L (1 county) • 0.4 mg/L (1 county) <u>Percentage of population in county with fluoridation</u> • <25% ○ *No. counties: 27* ○ *2ry bone cancer: 12.9%* ○ *Coefficient: ref*	secondary bone cancer from 2008 to 2010 at the county level in New York State

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size (N): 24,661 **Sex:** **Exclusions:** Patients with incomplete zip code, patient identification code, patient's New York State residency status or less than 18 years old **Source of funding/ support:**		Department of Health (NYSDOH)	○ *p-value: -* • 25%-75% ○ *No. counties: 16* ○ *2ry bone cancer: 12.9%* ○ *Coefficient: 0.02* ○ *p-value: 0.96* • >75% ○ *No. counties: 19* ○ *2ry bone cancer: 12.9 %* ○ *Coefficient: 0.02* ○ *p-value: 0.97*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Not reported **Author declaration of interest:** Not reported				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	**++**	Yes, participants were identified using the same method of ascertainment, recruited within the same time frame, and using the same inclusion and exclusion criteria

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	No accounting for confounders or appropriate standardization reported
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	There was no loss of participants due to attrition
Detection	Can we be confident in the exposure characterization?	++	• No information on whether individuals worked or went to school in a different county with a different water source, when they may have changed residences in their past or the degree to which the community fluoridation levels changed over time, or fluoride supplementation in counties without access to water fluoridation. • Study only assessed counties' municipal water fluoride content, excluding private wells and assuming their fluoride level to be zero.

Risk of bias assessment			
	Can we be confident in the outcome assessment?	++	Yes, outcome was assessed based on data on inpatient cancer patients admitted with an ICD9 code for secondary bone cancer (198.5) to a New York State hospital for relevant care, which was extracted from the Statewide Planning and Research Cooperative System (SPARCS) database; an inpatient/outpatient record of all hospital admissions collected and curated by New York State's Department of Health (NYSDOH)
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Fernando 2019 [93]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Case-control **Country:** Sri Lanka **Participants:** Cases: 19-76 years old, non-dialysis, biopsy-proven definite	**Exposures:** Fluoride level in serum **Method of exposure assessment:** ion-selective electrode (94-09 BNWP) with Orion Star A329 Ionalizer (Thermo Orion MA, USA) after dilution with an equal volume of commercially available TISAB III buffer (Thermo Orion 940911).	**Outcomes:** Chronic kidney disease of unknown origin (CKDu), using fluoride level in urine **Method of outcome ascertainment:** One hundred milliliters of a random urine sample from each subject was collected into sterile, screw-capped containers, and the supernatant was	**Statistical analysis:** • Descriptive statistics **Results:** • Water fluoride ○ *Fluoride in ground water: 1.33 - 5.30 mg/L* ○ *Fluoride MAC in drinking water: 0.60 mg/L* **Serum fluoride: Mean ±SD [range] mg/L** ○ *CKDu patients: 1.43 ± 1.2 [0.47 – 9.58]* ○ *Controls: 1.07 ± 0.3 mg/L [0.51 – 1.92]* ○ *p = 0.000 (showed a significant difference based on CKDu*	Higher fluoride exposure via drinking water is possibly the reason for higher fluoride in serum, while excessive urinary excretion would be due to deterioration of the kidney, suggesting a possible nephrotoxic role of environmental fluoride exposure.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
CKDu cases, recruited from Girandurukotte and Wilgamuwa renal clinics. Controls (matched): Healthy volunteers **Sampling time frame:** Nor reported **Sample size (N):** 193 (116 cases and 77 controls) **Sex:** Cases: Men (81.1%)		removed by centrifugation.	*stage but not with sex or age)* **Urinary fluoride: Mean ±SD [range] mg/L** ○ *CKDu patients: 1.53 ± 0.8 [0.45 – 6.92]* ○ *Controls: 1.26 ± 0.63 [0.36 – 3.80]* ○ *p = 0.004* • Patients in the age group 19–29 years showed lower serum fluoride levels than other age groups	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Controls: Men (70.1%) **Exclusions:** Not reported **Source of funding/ support:** National Research Council (NRC) Target Orient research Grant **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	+	Cases and controls were recruited from the same population, but with difference in age (cases older). No info on timeframe, ethnicity or eligibility criteria other than by outcome of interest
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	No accounting for confounding reported
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Yes, only one case was not included in the analysis

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	**++**	Serum and urine fluoride levels for all cases and controls were measured during the same timeframe and by the same ion-selective electrode method.
	Can we be confident in the outcome assessment?	**+**	Yes, the outcome was assessed in cases and controls using a confirmed biopsy and dialysis status. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	**++**	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	**++**	Descriptive analysis with no adjustment to potential confounders

Jimenez-Cordova 2019 [58]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Mexico (Chihuahua) **Participants:** 5-12 years old Mexican school children, who commonly drink tap water with a minimum of 2 years of residence in Hidalgo del Parral (fl:	**Exposures:** Fluoride levels in • Drinking water • Urine samples **Method of exposure assessment:** • Water samples were provided by each participant. • F concentrations in water and urine samples were assessed by a potentiometric method using an ion selective electrode (Orion 9609BNWP, Thermo Fisher Scientific Inc., USA); Del Razo et al., 1993. • F concentration in urine was measured by	**Outcomes:** • Vascular alterations using the carotid intima media thickness (cIMT) and serum concentrations of vascular adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), endothelin 1(ET-1) and cystatin-C (sCys-C) • Kidney dysfunction, using Kidney injury biomarkers [glomerular filtration rate (eGFR), and the urinary concentrations of kidney injury molecule 1 (KIM-1) and cystatin-C (uCys-C)]	**Statistical analysis:** • Multiple linear regression • Adjusted for urinary specific gravity, BMI, age and sex **Results:** • **Water fluoride:** Mean (IQR): ○ *0.3 mg/mL (0.01–1.9)* Maximum permissible limit: ○ *1.5* **Urinary fluoride showed**	• Fluoride exposure is related to early vascular alterations, which may increase the susceptibility of cardiovascular diseases in adult life. • Inconclusive results regarding fluoride exposure and kidney injury

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
0.18 mg/L) or Aldama (fl: 2 mg/L), where there is no concurrent exposure to arsenic **Sampling time frame:** November 2015 **Sample size (N):** 374 **Sex:** Boys: 46.8% **Exclusions:**	reference material (U-F-0907 and U-F1510), Centre de Toxicologie du Quebec) and controls were used for quality control. <u>Blood analysis</u> • Biochemical analysis (glucose, lipid profile, uric acid and creatine) was performed by an automatic analyser (Prestige 24i, Tokyo Boeki Medical System Ltd., Tokyo, Japan). <u>Urine analysis</u> • First morning void urine was used • Specific gravity was measured immediately using a refractometer (PAL-10S, ATAGO®, Tokyo, Japan)	**Method of outcome ascertainment:** • eGFR was determined by the Creatinine-Cystatin C-Based CKiD Equation (Schwartz et al., 2012) • Urine and serum biomarkers are measured using a custom human Magnetic Luminex Screening Assay (R&D Systems, Inc., Minneapolis MN, USA) that was read on a Luminex xMAP® Instrument (MAGPIX®, Luminex Corp., Austin TX, USA).	• Positive association with ○ *eGFR (β=1.3, p=0.015),* ○ *VCAM-1 (β=111.1, p=0.019)* ○ *ICAM-1 (β=57, p=0.032)* ○ *cIMT (β=0.01, p=0.032)* • Inverse association with ○ *uCys-C (β=−8.5, p=0.043)* ○ *sCys-C (β=−9.6, p=0.021)* • No significant association with ○ *ET-1 (β=0.069, p=0.074)* ○ *KIM-1 (β=29.1, p=0.212)*	

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Children with a previous diagnosis of chronic diseases **Source of funding/ support:** • Children's Environmental Health Network • National Council of Science and Technology, Mexico **Author declaration of interest:** No COI	• Urine analysis was performed with a urine analyser (U-66, Mindray Co., Shenzhen, China).			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	**++**	Yes, children were selected using the same criteria, and within the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	**++**	Yes, the analysis was adjusted for urinary specific gravity, BMI, age and sex
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	**++**	Not considered a risk of bias as it listed the exclusion was due to incomplete data or unavailability of samples

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	**++**	Yes, exposure was consistently assessed during the same timeframe and using the same tools for assessing fluoride levels in water and urine
	Can we be confident in the outcome assessment?	**++**	Yes, outcome was consistently measured in serum and urine. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	**++**	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	**++**	None identified

Jimenez-Cordova 2019a [59]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** Mexico **Participants:** Adult participants residing in Chihuahua for 1 or more years, were directly recruited from information sessions	**Exposures:** Fluoride levels in drinking water **Method of exposure assessment:** The Fluoride concentration in water and urine was assessed by a potentiometric method using an ion selective electrode (Orion 9609BNWP, Thermo Fisher Scientific Inc., USA).	**Outcomes:** Urinary concentrations of inorganic arsenic **Method of outcome ascertainment:** Concentrations were measured by hydride generation-cryotrapping-atomic absorption spectrometry using a Perkin Elmer Analyst 400 spectrometer (Perkin Elmer, Norwalk, CT) equipped with a multiatomizer as previously described	**Statistical analysis:** • Multiple linear regression • Adjusted for urinary specific gravity, age, sex, BMI and smoking **Results:** Water fluoride: *1.6 mg/L ±1.6* Urinary fluoride: *2.8* µg/L*±2.8* A statistically significant interaction of F and As exposure on the following was observed:	Fluoride exposure decreases Arsenic methylation capacity, and increases its toxicity

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: 2013 **Sample size (N):** 236 **Sex:** Men: 29% **Exclusions:** Non-residents of Chihuahua province **Source of funding/ support:**		(Hernández-Zavala et al., 2008).	• Increase in MAs% (β = 0.16, p = 0.018) • Decrease in DMAs% (β = −0.3, p = 0.034), • Decrease in PMI (β=−0.07, p=0.052) • Decrease in SMI (β=−0.13, p=0.097)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
National Council of Science and Technology, Mexico **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	**++**	Yes, participants were selected using the same criteria, during the same timeframe, and assessed for exposure and outcome using the same methods

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, the analysis was adjusted for urinary specific gravity, age, sex, BMI and smoking
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Not considered a risk of bias as it listed the reason for exclusion: non-residents of target location or unavailability of samples
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was consistently assessed during the same timeframe and using the same tools for assessing fluoride levels in water and urine
	Can we be confident in the outcome assessment?	++	Yes, outcome was consistently measured in urine. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were	++	None identified

Risk of bias assessment			
	appropriate and researchers adhered to the study protocol)?		

Khanoranga 2019 [60]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** Pakistan	**Exposures:** Fluoride levels in • Ground water samples • Urinary samples **Method of exposure assessment:** Ion selective electrode method	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Single dentist conducted DF examination using the WHO **Dean's** Index • CFI was calculated as: ∑ (Number of people x Dean numerical	**Statistical analysis:** • Relationship between fluoride level and DF was conducted using Pearson's correlation **Results:** • Correlation between groundwater fluoride levels and CFI r = 0.90	"The relationship among the groundwater fluoride concentration, urinary F, and dental fluorosis was assessed through Pearson's correlations. A strong positive relationship was

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Male brick kiln workers and controls (17 to 45 years of age) from three districts of Balochistan. Controls were office and university workers residing in locations with no fluoride exposure **Sampling time frame:** August – September 2017 **Sample size:** <u>Brick kiln workers</u> 100	**Exposure level:** Fluoride levels (mg/L) found in groundwater samples of the three districts (Quetta Pishin, and Mastung) • Range: 0.87 – 1.59 Mean (SD) Fluoride levels (mg/L) found in urinary samples of participants from the three districts and controls <u>Quetta (n = 25)</u> • Mean: 0.17 (0.15) • Range: 0.013 – 0.54 <u>Pishin (n = 50)</u>	weight) / Total number of people examined	• Correlation between urinary fluoride levels and CFI r = 0.96	determined by the aforementioned parameters (groundwater F, urinary F, and dental fluorosis)" (p. 419)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
<u>Controls</u> 20 **Sex:** Men: 100% **Exclusions:** NR **Source of funding / support:** NR **Author declaration of interest:** NR	• Mean: 0.19 (0.21) • Range: 0.002 – 0.842 <u>Mastung (n = 25)</u> • Mean: 0.30 (0.19) • Range: 0.092 – 0.811 <u>Control (n = 20)</u> • Mean: 0.003 (0.002) • Range: 0.0003 – 0.007			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	NR
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the US-EPA ion selective electrode (CRISON, GLP 22+).

Risk of bias assessment			
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by a single dentist using the WHO Dean's Index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Liu 2019 [61]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type:	**Exposures:**	**Outcomes:**	**Statistical analysis:**	• low-to-moderate fluoride exposure is associated with

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Original study **Study design:** Cross-sectional **Country:** China **Participants:** Randomly selected 7–13 years old residents from low to-moderate fluorosis, ground water-supplied areas of Baodi District, Tianjin, China	Fluoride levels in ground water and urine **Method of exposure assessment:** concentrations of Fluoride in water samples and morning urine samples were measured by ion selective electrode (PF-202-CF, INESA, Shanghai) using the national standardized method in China (WS/T 89−2006) (Wu et al., 2015; Yu et al., 2018)	age- and sex-standardized height, weight and BMI z-scores, and childhood overweight/obesity (BMI z-score > 1) **Method of outcome ascertainment:** • Study entry standardized anthropometric survey by a trained investigator without knowledge of the children's fluoride levels. • Height was measured using a stadiometer, and weight was measured using a standard dual reading scale.	• Multivariable linear and logistic regression analyses • Adjusted for maternal age at delivery, second hand tobacco smoke, maternal education, paternal education, household income, child age, gender and low birth weight • Sensitivity analysis conducted after excluding children born to women with smoking, drinking, diabetes, under-nourishment and anaemia at pregnancy, and children with dystocia, hypoxia, premature birth and post-term birth **Results:** • Water fluoride: ○ *0.83 mg/L (95%CI: 0.81, 0.86)*	overweight and obesity in children. • Gender and paternal education level may modify the relationship

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: May - October 2015 **Sample size (N):** 2,430 **Sex:** Boys: 51.1% **Exclusions:** • History of chronic medical illness (e.g. renal, hepatic, and endocrine disorders), • Long-term medication related to overweight and obesity were not included		• Standardized specific z-scores were calculated using WHO's Child Growth standards, and for weight using CDC's reference standards (WHO standards are unavailable for this age group)	○ *p-value: 0.414* • Urinary fluoride ○ *0.43 mg/L (95%CI: 0.41, 0.46)* ○ *p-value: 0.003* • linear dose-dependent positive association between water fluoride levels and height z-score, as indicated by the trend across fluoride quartiles (Ptrend=0.022). • Each log unit (roughly 10-fold) increase in urinary fluoride concentration was associated with a ○ *0.136 unit increase in weight z-score (95% CI: 0.039, 0.233)* ○ *0.186 unit increase in BMI z-score (95% CI: 0.058, 0.314)* ○ *1.304-fold increased odds of overweight/obesity*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding/ support: • National Natural Science of China • National Natural Science Foundation of China • Fundamental Research Funds for the Central Universities **Author declaration of interest:** No COI			*(95% CI: 1.062, 1.602)* ○ *These associations were stronger in girls than in boys (P interaction= 0.016)* ○ *Children of fathers with lower education levels were more vulnerable to fluoride (P interaction=0.056)* • Each log unit (roughly 10-fold) increase in water fluoride concentration was associated with a 0.129 unit increase in height z-score (95% CI: 0.005, 0.254), but not with other anthropometric measures.	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected at random from the same areas, using the same criteria and during the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as maternal age at delivery, second hand tobacco smoke, maternal education, paternal education, household income, child age, gender and low birth weight
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Not considered a risk of bias as it listed the exclusion was due to those with extremes of BMI scores

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was consistently assessed during the same timeframe and using the same tools for assessing fluoride levels in water and urine
	Can we be confident in the outcome assessment?	++	Yes, outcome was consistently assessed by a trained investigator without knowledge of the children's fluoride levels, in accordance with WHO and CDC standards
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Malin 2019 [62]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** United States **Participants:** US adolescents: 12–19 years old (NHANES survey) **Sampling time frame:**	**Exposures:** Fluoride in drinking water and serum **Method of exposure assessment:** • Water samples were measured via an ion-specific electrode • Plasma fluoride was measured via an ion-specific electrode and hexamethyldisiloxane (HMDS) method • Tap water and blood collection times were not standardized	**Outcomes:** • Estimated glomerular filtration rate • Serum uric acid • Albumin to creatinine ratio • Blood urea nitrogen • AST/ALT • ALP • Gamma-glutamyl transferase • Serum albumin **Method of outcome ascertainment:** • Serum was analyzed for markers of kidney and liver function as part of a standard biochemistry profile. From 2013 to 2016 a Beckman Coulter UniCel DxC 800 Synchron chemistry	**Statistical analysis:** • Multiple linear regression • Adjusted for age, sex, race, BMI, family income, daily protein intake and serum cotinine (biomarker of tobacco smoke exposure) **Results:** • Tap water fluoride *0.48 mg/L ± 0.03* • Plasma fluoride *0.40 µmol/L ± 0.01* • A 1 mg/L increase in water fluoride was associated with: ○ *0.93 mg/dL lower blood urea nitrogen concentration (95%*	Fluoride exposure may contribute to complex changes in kidney and liver related parameters among US adolescents

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
2013–2016 **Sample size (N):** 4,470 **Sex:** Men: 52.7% **Exclusions:** • Institutionalized persons • Suggestive kidney diseases • Not drinking tap water • insufficient or excessive protein intake		analyzer was utilized; while from 2015 to 2016 a Beckman Coulter UniCel DxC 660i Synchron Access chemistry analyzer was utilized as well. • Urine samples were analyzed for albumin and creatinine using a Turner Digital Fluorometer, Model 450 and Roche Cobas 6000 Analyzer respectively. Urine sample collection time was not standardized.	*CI: −1.44, −0.42; p=0.007).* ○ *eGFR: -1.03 mL/min/m2 (95% CI: -2.93, 0.87); p > 0.99; water fluoride was log2 transformed in this model.* ○ *SUA: 0.05 mg/dL (95% CI: -0.07, 0.18); p > 0.99* ○ *ACR: -0.01 mg/g (95% CI: -0.07, 0.06); p = > 0.99; water fluoride and outcome variables were log2 transformed.* • 1 µmol/L increase in plasma fluoride was associated with: ○ *10.36 mL/min/1.73m2 lower estimated glomerular filtration rate (95% CI: −17.50, −3.22; p=0.05)* ○ *0.29 mg/dL higher serum uric acid concentration (95%*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding/ support: • Mount Sinai Children's Center Foundation • NIH/NIEHS **Author declaration of interest:** No COI			○ *CI: 0.09, 0.50; p=0.05)* ○ *1.29 mg/dL lower blood urea nitrogen concentration (95%CI: −1.87, −0.70; p < 0.001)*	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	

Risk of bias assessment					
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected using the same criteria, during the same timeframe		
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, sex, race, BMI, family income, daily protein intake and serum cotinine (biomarker of tobacco smoke exposure)		
Performance	Were experimental conditions identical across study groups?	N/A			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A			
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (institutionalized persons, kidney diseases, not drinking tap water and insufficient or excessive protein intake), which were not related to the outcome		
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was consistently measured in serum and urine using gold standard tests.		
	Can we be confident in the outcome assessment?	++	Yes, outcome (kidney dysfunction) was consistently measured in serum and urine. Lack of	+	Outcome (liver dysfunction) was consistently assessed with results showing no correlation (human

Risk of bias assessment					
			blinding of outcome assessors would not appreciably bias results.		evidence) but reported as having correlation with exposure (based on animal evidence)
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Malin 2019a [63]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposures:** Fluoride level in drinking water and serum	**Outcomes:** Self-reported sleep	**Statistical analysis:** • Survey-weighted linear and multinomial logistic regression analyses	Fluoride exposure may contribute to changes in sleep

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Cross-sectional **Country:** US **Participants:** 16-19 years old adolescents with fluoride biomonitoring data and self-reported sleep outcome measures (NHANES 2015–2016) **Sampling time frame:**	**Method of exposure assessment:** • Fluoride concentrations were measured in blood plasma and household tap water. • Collection times of blood and tap water were not standardized • Plasma fluoride concentrations were measured using an ion-specific electrode and hexamethyl-disiloxane method • Tap water samples were measured electrometrically with an ion-specific electrode	outcome measures **Method of outcome ascertainment:** • Sleep habits and sleep disorders were ascertained through questionnaires in participants' homes by trained staff using the Computer-Assisted Personal Interview (CAPI) system. • The questions included in the sleep questionnaire were not validated	• Adjusted for age, sex, body mass index (BMI), race/ethnicity, and the ratio of family income to poverty **Results:** • **Tap water fluoride mean (SE):** *0.39 mg/L (0.05)* • **Plasma fluoride mean (SE):** *0.35 µmol/L (0.02)* Median (IQR) for: • Water fluoride: *0.27 (0.52) mg/L* • Plasma fluoride *0.29 (0.19) µmol/L*	cycle regulation and sleep behaviors among older adolescents in the US.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
2015–2016 **Sample size (N):** 419 **Sex:** Men: 49.08 **Exclusions:** • Not consuming tap water • Consuming sleep medications • No fluoride samples **Source of funding/ support:** NIH/NIEHS			• An IQR increase in water fluoride was associated with ○ *1.97 times higher odds of reporting symptoms suggestive of sleep apnea (95% CI: 1.27, 3.05; p = 0.02)* ○ *24 min later bedtime (B = 0.40, 95% CI: 0.10, 0.70; p = 0.05)* ○ *26 min later morning wake time (B = 0.43, 95% CI: 0.13, 0.73; p =0.04)* ○ *Among males, a 38% reduction in the odds of reporting snoring (95% CI: 0.45, 0.87, p =0.03).*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected using the same criteria, during the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, sex, body mass index (BMI), race/ethnicity, and the ratio of family income to poverty
Performance	Were experimental conditions identical across study groups?	N/A	

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Not considered a risk of bias as study documented the reasons for exclusion of participants (not drinking tap water, consuming sleep medications, and lack of plasma or water samples)
Detection	Can we be confident in the exposure characterization?	+	Yes, exposure was consistently measured in serum and urine. However, the questions included in the sleep questionnaire were not validated.
	Can we be confident in the outcome assessment?	++	Yes, outcome was consistently measured in serum and urine. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Pei 2019 [64]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** China **Participants:** Residents aged 16 or older who lived in one of five villages that are endemic in skeletal	**Exposures:** • Fluoride levels in drinking water • Skeletal fluorosis **Method of exposure assessment:** • Fluoride levels in drinking water, blood, and urine samples • Fluoride in drinking water was detected by a F-ion selective electrode (Yingke Crystal Materials Company) using a China national standard (GB 5750.5-2006, China). • Urinary fluoride was also assessed by using	**Outcomes:** Genetic biomarkers of skeletal fluorosis **Method of outcome ascertainment:** • Serum miRNAs were extracted with miRNeasy Mini Kit (Qiagen, Valencia, CA, USA). • After assessing the RNA's quality and quantity, the miRNA microarray analysis (Affymetrix microRNA 4.0 Array, Santa Clara, CA, USA) was performed according to the manufacturer's instructions.	**Statistical analysis:** • Descriptive statistics **Results:** • Water fluoride groups: ○ *1.2 mg/L* ○ *>1.2 mg/L - ≤2 mg/L* ○ *>2 mg/L - ≤4 mg/L* ○ *>4 mg/L* • 31 miRNAs were significantly and differentially expressed between cases and controls. Of these, 21 miRNAs were up-regulated and 10 miRNAs were down-regulated • 3 additional miRNAs (miR-200c-3p, miR-	• Multiple signaling pathways were found to be regulated by the differentially expressed miRNAs • Dysregulation of molecular signaling pathways are involved in the process of fluoride-induced damage of osteoblasts and osteoclasts. However, the regulatory mechanism of fluoride on molecular pathways is still not very clear

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
fluorosis, (Zhao Dong County, Heilongjiang Province) **Sampling time frame:** NR **Sample size (N):** 302 **Sex:** Men: 30% **Exclusions:** • Bone diseases • Hypertension • Atherosclerosis	the standard (WS/T 89–2015, China). • Skeletal fluorosis was diagnosed using the national diagnostic standard for endemic skeletal fluorosis (WS192-2008) • Subjects were investigated using a questionnaire, and were face-to-face interviewed by well-trained staff. • Every subject received a clinical examination, including X-ray investigation	• Quantitative PCR was performed using a TaqMan miRNA PCR kit (Haigene, Harbin, China) on an ABI7500 Fast Realtime PCR system (ABI, USA).	1231 and miR-3185) were significantly up-regulated in the cases	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Heart disease • Diabetes **Source of funding/ support:** • National Natural Science Foundation of China • Translational Medicine Special Foundation of China-Russia Medical Research Center • Harbin Medical University, China • Science Foundation for Distinguished Young Scholars of Heilongjiang Province, China **Author declaration of interest:**				

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	+	Whereas participants were selected using the same criteria, recruitment time frame was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	−−	Not reported
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	There was no attrition of exclusion of participants from the analysis in this study

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Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was consistently measured in drinking water, blood, and urine samples using national standard tests
	Can we be confident in the outcome assessment?	++	Yes, outcome was assessed using national standards. Lack of blinding of assessors of skeletal fluorosis does not seem to appreciably bias results
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Riddle 2019 [65]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design** Cross-sectional study **Country** Canada **Participants** Persons Youth 6-17 years old from the North American Health Measures Survey (Cycles 2 and 3). **Study name**	**Exposures** <u>Fluoride levels in</u> • Community source • Tap water • Urine **Method of exposure ascertainment** <u>Community water fluoridation status (CWF)</u> Acquired from city website reports or water treatment plant <u>Urinary fluoride (UF_{SG}):</u> non-fasting spot samples	**Outcome** Attention-related outcomes **Method of outcome ascertainment** • Attention deficit hyperactivity disorder (ADHD) diagnosed by physician • Hyperactivity/inattention subscale score acquired using Strengths and Difficulties Questionnaire (SDQ) • Information on both outcomes were acquired from parents/guardians for participants 6 to 11 years of age • Among those 12 to 17 years of age,	**<u>Statistical analysis:</u>** • Logistic regression to examine the associations between fluoride exposure measure (UF_{SG}, CWF, tap water) and ADHD • Linear regression used, with the same covariates to examine the associations between the (UF_{SG}, CWF, tap water) and SDQ hyperactivity/inattention subscale score. • Adjusted covariates: sex, age, ethnicity, BMI, highest parental education, household income, cigarette smoke exposure at home, and log_{10}-transformed lead level in blood)	• Higher tap water fluoride levels were associated with a higher risk of ADHD and increased symptoms of hyperactivity and inattention, especially among adolescents. • Tap water fluoride concentration was significantly associated with ADHD, adjusting for covariates

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• North American Health Measures Survey (CHMS) **Sampling timeframe** • 2009–2011 • 2012–2013 **Sample size (N)** • Cycle 2: N=2,520 • Cycle 3: N=2,667 **Sex (%)** Men: 50.8%–52.7% **Exclusion criteria** • Resided in home for ≤ 2 years • Reside in place with mixed city fluoridation	<u>Tap water fluoride</u> Samples from participants' home during Cycle 3 **Mean (SD) concentration of urinary fluoride adjusted for specific gravity (mg/L)** • <u>Urinary fluoride – sample 1</u> 0.61 (0.39) • <u>CWF status - sample 2</u> 0.64 (0.45) • <u>Tap water fluoride – sample 3</u> • 0.62 (0.48)	outcome information was acquired from the participants themselves	**Results** • **Water fluoride** *Mean ±SD: 0.23 mg/L ±0.24 (cycles 3 only)* • **Urinary fluoride** *Mean ±SD: 0.61 mg/L ±0.39 (cycles 2 & 3)* • An increase of 1.0 mg/L in water fluoride concentration was associated with 6.1 times higher odds of an ADHD after accounting for potential confounders • UF_{SG} did not significantly predict ADHD *aOR=0.96 (95% CI: 0.63, 1.46); p=0.84*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
status Consume bottled water • Consume well rather than municipal water • Remove fluoride with home filtration system **Source of funding:** Faculty of Health, York University **Conflict of interest:** No COI	**Mean (SD)** **concentration of water fluoride (mg/L)** • Urinary fluoride – sample 1 0.23 (0.24) • CWF status – sample 2 0.26 (0.26) • Tap water fluoride – sample 3 0.23 (0.24) **Mean (SD)** • Urinary fluoride 11.3 (3.4) • CWF status 11.3 (3.3) • Tap water fluoride 11.2 (3.5)		• UF_{SG} did not significantly predict SDQ hyperactive/ inattentive subscale scores *aOR = 0.31 (-0.04, 0.66); p = 0.08* • An increase of 1.0 mg/L in water fluoride concentration was associated with 6.1 times higher odds of an ADHD after adjusting for potential confounders • UF_{SG} did not significantly predict ADHD *aOR=0.96 (95% CI: 0.63, 1.46); p=0.84*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• UF_{SG} did not significantly predict SDQ hyperactive/ inattentive subscale scores aOR = *0.31 (-0.04, 0.66); p = 0.08* <u>ADHD diagnosis & tap water fluoride</u> • aOR = 6.10 (1.60, 22.8); p < 0.05 • Exposure-response relationship: yes <u>SDQ hyperactive/inattentive subscale score & tap water fluoride</u> • aOR = 0.31 (0.04, 0.58); p < 0.05	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Exposure-response relationship: yes <u>ADHD diagnosis &</u> <u>UF_{SG}</u> • aOR = 0.96 (0.63, 1.46); p < 0.05 • Exposure-response relationship: yes <u>SDQ</u> <u>Hyperactive/Inattentive</u> <u>Subscale Score & UF_{SG}</u> • aOR = 0.31 (-0.04, 0.66); p = 0.05 Exposure-response relationship: yes	

Risk of bias assessment		
Bias domain	***Criterion***	***Response***

Risk of bias assessment			
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	**++**	Participants who lived in private households across Canada were randomly selected from Cycle 2 (2009–2011) and Cycle 3 (2012–2013) of the CHMS.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	**++**	Yes (child's sex, age at interview, ethnicity (white or other), BMI, highest level of parental education, total household income, smoking at home [yes/no], concurrent blood lead level [log10-transformed], specific gravity of urinary fluoride concentration)
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	**++**	Not considered a risk of bias as it documented the exclusion of those who reported drinking bottled water as

Risk of bias assessment			
			their main source of water, or those who lived in their residence location for less than 3 years.
Detection	Can we be confident in the exposure characterization?	++	Yes, urinary fluoride was measured in non-fasting spot samples, adjusted for specific gravity (UFSG), and analyzed using an Orion PH meter with a fluoride ion selective electrode after being diluted with an ionic adjustment buffer. Samples were not standardized though with respect to collection time.
	Can we be confident in the outcome assessment?	++	Yes, hyperactivity/inattention subscale score from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001) and a physician-made diagnosis of ADHD were measured for all participants in both Cycles 2 and 3 of the CMHS.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods	++	None identified

Risk of bias assessment			
	were appropriate and researchers adhered to the study protocol)?		

Shaik 2019 [66]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** India	**Exposures:** Fluoride levels in drinking water **Method of exposure assessment:** • Water analysis was carried out using OAKTON Fluoride Ion Selective Electrode Equipment, USA.	**Outcomes:** Thyroid function biomarkers (TSH, T3, T4 in serum) **Method of outcome ascertainment:** • Serum T3, T4 was determined with Competitive Chemi Luminescent Immunoassay kits	**Statistical analysis:** • Descriptive analyses **Results:** • **Water fluoride mean:** *Group I (0.01-0.6 ppm): 0.22* *Group II (0.7-1.2 ppm): 0.89* *Group III (1.3-2.0 ppm): 1.44*	Long term intake of fluoridated drinking water (0.02 -1.4 ppm) did not show effect on the thyroid function in the children with normal nutritional status and optimal iodine intake

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Children 9-13 years old with lifelong residence in one of 19 villages in Mysore Taluk, with water fluoride levels 0.01-1.8 ppm). Children must have had good general health, normal nutritional status, and were consuming Iodized salt **Sampling time frame:** NR **Sample size (N):** 293		• Serum TSH was determined with Ultra-Sensitive Sandwich Chemi-Luminescent Immunoassay with analyzer according to the manufacturer recommendation.	• TSH: 40% of children of group I had deranged levels followed by group III (20%) and Group II (16%) • T4: 24% of children of both groups I and III had deranged levels followed by group II (20%) • Inter group correlation of drinking water fluoride levels to number of deranged serum T3, T4, and TSH of the children showed non-significant association	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: Boys: 46% **Exclusions:** Non-resident children, and those with substandard growth or health status **Source of funding/ support:** NR **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	+	Whereas participants were selected using the same criteria, recruitment time frame was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	−−	Not reported
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	There was no attrition of exclusion of participants from the analysis in this study
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was consistently measured in drinking water using specialized tests
	Can we be confident in the outcome assessment?	++	Outcome was assessed using specialized standards. Study was double-blinded with no likelihood to bias results.

Risk of bias assessment			
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Soto-Barreras 2019 [67]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study	**Exposures:** Fluoride levels in • Drinking water samples • Urine samples	**Outcome(s):** • Intellectual ability • Dental fluorosis **Method of outcome ascertainment:**	**Statistical analysis:** • Statistical significance at $p<0.05$ **Results:** • Mean (±SD) water fluoride levels (mg/L) by	• "No evidence was found for fluoride-associated cognitive deficits. As the level of fluoride consumption remains a public health concern and its implications for

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Mexico **Participants:** Children (9 to 10 years of age) in grade 4 attending public elementary schools in Chihuahua **Sampling time frame:** May – December 2017 **Sample size:** 161	**Method of exposure assessment:** • Ion selective electrode **Exposure level:** See results for exposure levels by dental fluorosis and intellectual ability categories	• Intellectual ability: Raven's Colored Progressive Matrices (RCPM) Dental fluorosis: Thylstrup-Fejerskov (TF) Index used to examine vestibular, occlusal, and lingual surfaces	dental fluorosis categories ○ *TF 0: 0.75 ± 0.95* ○ *TF 1 – 2: 0.67 ± 0.15* ○ *TF 3 – 4: 1.22 ± 1.09* ○ *TF > 5: 1.66±0.93* ○ *p–value: 0.008* • Mean (±SD) urinary fluoride levels (mg/L) by dental fluorosis categories ○ *TF 0: 0.48 ± 0.23* ○ *TF 1 – 2: 0.51 ± 0.38* ○ *TF 3 – 4: 0.62 ± 0.32* ○ *TF > 5: 0.67±0.41* ○ *p-value: 0.088* • Mean (±SD) exposure dose to fluoride (EDI) (mg/kg bw/day) by dental fluorosis categories ○ *TF 0: 0.016 ± 0.02* ○ *TF 1 – 2: 0.017 ± 0.02* ○ *TF 3 – 4: 0.035 ± 0.03* ○ *TF > 5: 0.047±0.03*	health are still uncertain, further research is needed to clarify whether or not fluoride may possibly have adverse effects on brain development." (p. 481) • "The fluoride content in the drinking water and the exposure dose were significantly higher in the moderate-to-severe fluorosis cases. The urinary fluoride level increased as the level of the severity of the dental fluorosis increased but no statistically significant

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: Men: 88 (54.7%) **Exclusions:** • Received topical fluoride application in last 6 months • Have different residence since time of pregnancy • Have mental illness diagnosis • Have systemic disorder diagnosis **Source of funding / support:**			○ *p-value: 0.001* • Mean (±SD) water fluoride levels (mg/L) by IQ categories ○ *Grade I: 1.48 ± 1.13* ○ *Grade II: 1.05 ± 1.06* ○ *Grade III: 1.04 ± 1.06* ○ *Grade IV: 0.97 ± 1.10* ○ *Grade V: 0.79 ± 1.17* ○ *p–value: 0.645* • Mean (±SD) urinary fluoride levels (mg/L) by IQ grade categories ○ *Grade I: 0.45 ± 0.34* ○ *Grade II: 0.54 ± 0.29* ○ *Grade III: 0.61 ± 0.38* ○ *Grade IV: 0.56 ± 0.33* ○ *Grade V: 0.35 ± 0.19* ○ *p–value: 0.559* • Mean (±SD) exposure dose/daily intake by IQ grade categories	difference was present." (p. 477 – 478)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
PRODEP program of the Mexican Minister of Education (SEP) **Author declaration of interest:** No COI			○ *Grade I: 0.03 ±0.03* ○ *Grade II: 0.026 ±0.03* ○ *Grade III: 0.027 ±0.03* ○ *Grade IV: 0.029 ±0.03* ○ *Grade V: 0.016 ±0.02* ○ *p–value: 0.389*	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable

Risk of bias assessment					
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.		
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR		
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable		
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable		
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (received topical fluoride application in last 6 months, have different residence since time of pregnancy, have mental illness diagnosis, or have systemic disorder diagnosis)		
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the ion selective electrode (Orion 9609BNWP, Ionplus Sure-Flow Fluoride Electrode, Thermo Scientific, USA)		
	Can we be confident in the outcome assessment?	++	Yes, outcome (IQ/intellectual ability)	++	Yes, outcome (dental fluorosis) was measured

Risk of bias assessment					
			was measured by an independent examiner, using the Raven's Colored Progressive Matrices (RCPM). Lack of blinding of outcome assessors would not appreciably bias results.		by a single examiner, assisted by a recorder, using the Thysltrup and Fejerskov Index. Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Zhang 2019 [68]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:** US **Participants:** Massachusetts (MA) resident women with a live birth (2009- 2016) who responded to the PRAMS survey	**Exposures:** • Dental cleaning during pregnancy (DC) alone • Community water fluoridation (CWF) alone • DC and CWF combined **Method of exposure assessment:** • DC: PRAMS survey questionnaire • CWF: MA Dept. of Public Health, Office of Oral Health	**Outcomes:** Prevalence of preterm births (birth < 37 weeks gestation) **Method of outcome ascertainment:** Derived from the infant's birth certificate	**Statistical analysis:** • Multivariate logistic regression • Adjusted for maternal sociodemographic characteristics (age, race, nativity, education, income, health insurance), previous medical risk (diabetes, preterm births) and behavioral factors (BMI) **Results:** • Water fluoride levels: NR • Prevalence of preterm birth among women with a singleton live birth was 8.5% in Massachusetts.	Women who had dental cleaning during pregnancy and lived in a community with water fluoridation had lower prevalence of preterm birth.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
(Pregnancy Risk Assessment Monitoring System) **Sampling time frame:** 2009-2016 **Sample size (N):** 9,234 **Sex:** Women: 100% **Exclusions:** • Women with multiple births			• Overall, 58.7% of women had dental cleaning during pregnancy, and 63.6% lived in CWF. • Compared to women without DC and CWF and adjusting for potential confounders: ○ *Dental cleaning alone and preterm birth: significant (aRR = 0.74 [95% CI 0.55–0.98])* ○ *CWF alone and preterm birth: non-significant (aRR = 0.81 [95% CI 0.63–1.05])* ○ *DC–CWF and preterm birth: significant (aRR = 0.74 [95% CI 0.57–0.95]) were significant*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Missing data for dental cleaning during pregnancy, CWF, and/or gestational age • Missing data on relevant maternal characteristics **Source of funding/ support:** CDC **Author declaration of interest:** NR				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected using the same criteria, during the same timeframe
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as maternal sociodemographic characteristics (age, race, nativity, education, income, health insurance), previous medical risk (diabetes, preterm births) and behavioral factors (BMI)
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Not considered a risk of bias as study reported that nonresponse adjustment factors were incorporated to address the increased likelihood of non-response from certain groups of women, such as those who had < 12 years of education.

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was consistently measured using the PRAMS survey questionnaire (DC), and the MA Dept. of Public Health records (CWF)
	Can we be confident in the outcome assessment?	++	Yes, outcome was retrieved from state infant birth certificates
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Zhou 2019 [69]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposures:**	**Outcomes:**	**Statistical analysis:**	• High intake of fluoride may act directly and/or

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Cross-sectional **Country:** China **Participants:** Residents (for ≥10 years) of the Han nationality in 1 of 12 villages in north east China, aged ≥40 years old, with no congenital eye disease or ocular trauma	Fluoride levels in drinking water **Method of exposure assessment:** Fluoride levels in the blood, urine, and drinking-water	Prevalence of one of seven eye diseases **Method of outcome ascertainment:** Complete ocular examination	• Multiple logistic regression analysis • Adjusted for age, smoking, drinking habits, blood pressure, BMI, education, and annual income. **Results:** • Drinking-water fluoride: >1.2 mg/L • Fluoride in the drinking water was closely associated with: ○ *Cataract: OR: 0.543 (95% CI 0.310–0.845).* ○ *Pterygium: OR: 1.991 (95% CI 1.931–3.622).* ○ *Arteriosclerotic retinopathy: OR: 2.011 (95% CI 1.121–3.637).* ○ *Primary angle closure glaucoma:*	indirectly on the eyeball. • Significant positive association of water fluoride levels with pterygium and arteriosclerotic retinopathy, and significant inverse association with cataract. • Non-significant associations with primary angle closure glaucoma, diabetic retinopathy, age-related macular degeneration, and strabismus.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: NR **Sample size (N):** 1,813 **Sex:** Men: 30% **Exclusions:** • Less than 10 years of residence • congenital eye disease or ocular trauma **Source of funding/ support:**			*OR:1.179 (95% CI: 0.788–1.489).* ○ *Diabetic retinopathy: OR: 1.845 (95% CI: 0.931–3.120).* ○ *Age-related macular degeneration: OR: 1.048 (95% CI: 0.735–2.221).* ○ *Strabismus: OR: 1.598 (95% CI: 0.936–2.689).* • Compared to the control group: ○ *Significant decrease for cataract (14.9% in exposed group, 24.7% in control group)* ○ *Significant increases for pterygium (7.7% in exposed group, 3.2% in control group)* ○ *Significant increases for arteriosclerotic retinopathy (17.6% in*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Center for Endemic Disease Control • Chinese Center for Disease Control and Prevention **Author declaration of interest:** No COI			*exposed group, 6.4% in control group).* ○ Non-significant associations with primary angle closure glaucoma, diabetic retinopathy, age-related macular degeneration, and strabismus	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	
	Was allocation to study groups adequately concealed?	N/A	
	Did selection of study participants result in appropriate comparison groups?	+	Whereas participants were selected using the same criteria, recruitment time frame was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Except for gender (P<0.001), there was no significant difference between the two groups (exposed vs

Risk of bias assessment			
			control) for the other the confounders such as age, smoking and drinking habits, blood pressure, body mass index, education, and the annual income.
Performance	Were experimental conditions identical across study groups?	N/A	
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	There was no attrition of exclusion of participants from the analysis in this study
Detection	Can we be confident in the exposure characterization?	+	Whereas the exposure was measured in drinking water, serum and urine, no information was provided on the methods/tests used in that regard
	Can we be confident in the outcome assessment?	+	Outcome was assessed using standard examinations. With no information provided, lack of blinding might have an impact on ocular assessments conducted on study participants.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Zhou 2019a [70]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** China	**Exposures:** Fluoride levels in • Drinking water samples • Urine samples **Method of exposure assessment:**	**Outcome(s):** • Genotoxicity (Mitochondrial DNA (mtDNA) levels) • Dental fluorosis (DF) **Method of outcome ascertainment:** • mtDNA: quantitative real-time polymerase chain reaction assay	**Statistical analysis:** • Multivariable linear and logistic regression models • Fluoride categorized into tertiles (T) • Association of mtDNA with water and urinary fluoride levels were adjusted for age, gender, BMI, LBW, maternal education, paternal education, and family income	"In conclusion, we have showed that low-to-moderate concentrations of water fluoride and urinary fluoride were positively associated with DF prevalence, while inversely

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Children (7 to 13 years to age), from rural areas with low-to-moderate fluoride exposure in Tianjin **Sampling time frame:** 2015 **Sample size:** 616 **Sex N (%):** <u>Non-DF group</u>	• National standardized ion selective electrode method **Exposure level in mg/L (P25 – P75):** <u>Non-DF group</u> • Water: 0.70 (0.40 – 0.80) • Urine: 0.17 (0.09 – 0.31) <u>DF group</u> • Water: 1.60 (1.20 – 2.60) • Urine: 2.11 (0.45 – 2.69)	• <u>DF</u>: Dean's classification system. Two independent experts conducted each examination. DF index was determined using the most serious form of fluorosis on ≥ 2 teeth	• Association of DF with water and urinary fluoride levels were adjusted for age, gender, BMI, LBW, maternal education, paternal education, and family income **Results:** ***mtDNA*** • Change (95% CI) in mtDNA levels among those with water fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.70)</u> Reference <u>T2 (0.71 – 1.50)</u> B = -0.24 (-0.32, -0.15) P = 0.035 <u>T3 (> 1.50)</u> B = -0.32 (-0.39, -0.24)	associated with circulating mtDNA levels. Additionally, our study indicates that the gender potentially modifies the associations of DF prevalence with relative mtDNA levels and low-to-moderate fluoride exposure, and that the reduced mtDNA levels may partly mediate the elevated prevalence of moderate DF in

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Men: 109 (45.4%) <u>DF group</u> Men: 202 (53.7%) **Exclusions (from analysis):** • Have cavities • Have orthodontic appliances **Source of funding / support:** • The State Key Program of National Natural Science of China • The National Natural Science Foundation of China			P <0.001 <u>Trend test</u> P <0.001 • Change (95% CI) in mtDNA levels per 1 mg/L increase in water fluoride level B = -0.10 (-0.14, -0.06) P <0.001 • Change (95% CI) in mtDNA levels among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.21)</u> Reference <u>T2 (0.22 – 2.08)</u> B = -0.03 (-0.12, 0.06) P = 0.516 <u>T3 (> 2.08)</u> B = -0.27 (-0.35, -0.20) P <0.001	children under such exposure.”

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
The Fundamental Research Funds for the Central Universities **Author declaration of interest:** NR			<u>Trend Test</u> P <0.001 • Change (95% CI) in mtDNA levels per 1 mg/L increase in urinary fluoride level B = -0.12 (-0.14, -0.09) P <0.001 ***Total DF*** • Odds (95% CI) of total DF among those with water fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.70)</u> Reference <u>T2 (0.71 – 1.50)</u> OR = 2.58 (2.02, 3.30) P <0.001 <u>T3 (> 1.50)</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			OR = 3.64 (2.91, 4.55) P <0.001 <u>Trend Test</u> P <0.001 • Odds (95% CI) of total DF per 1 mg/L increase in water fluoride level OR = 1.47 (1.40, 1.55) P <0.001 • Odds (95% CI) of total DF among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.21)</u> Reference <u>T2 (0.22 – 2.08)</u> OR = 1.49 (1.26, 1.77) P <0.001 <u>T3 (> 2.08)</u> OR = 3.16 (2.53, 3.95)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			P <0.001 <u>Trend Test</u> P <0.001 • Odds (95% CI) of total DF per 1 mg/L increase in urinary fluoride level OR = 1.39 (1.32, 1.46) P <0.001 ***Very Mild DF*** • Odds (95% CI) of very mild DF among those with water fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.70)</u> Reference <u>T2 (0.71 – 1.50)</u> OR = 2.33 (1.55, 3.51) P <0.001 <u>T3 (> 1.50)</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			OR = 4.93 (3.48, 6.98) P <0.001 <u>Trend Test</u> P <0.001 • Odds (95% CI) of very mild DF per 1 mg/L increase in water fluoride level OR = 1.85 (1.63, 2.11) P <0.001 • Odds (95% CI) of very mild DF among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.21)</u> Reference <u>T2 (0.22 – 2.08)</u> OR = 1.31 (0.92, 1.86) P = 0.135 <u>T3 (> 2.08)</u> OR = 4.02 (2.81, 5.74)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			P <0.001 <u>Trend Test</u> P <0.001 • Odds (95% CI) of very mild DF per 1 mg/L increase in urinary fluoride level OR = 1.57 (1.41, 1.76) P <0.001 ***Mild DF*** • Odds (95% CI) of mild DF among those with water fluoride levels in T2 and T3 compared to T1 (mg/L) <u>T1 (≤ 0.70)</u> Reference <u>T2 (0.71 – 1.50)</u> OR = 4.17 (2.80, 6.20) P <0.001	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			T3 (> 1.50) OR = 6.88 (4.78, 9.92) P <0.001 Trend Test P <0.001 • Odds (95% CI) of mild DF per 1 mg/L increase in water fluoride level OR = 1.68 (1.57, 1.79) P <0.001 • Odds (95% CI) of mild DF among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) T1 (≤ 0.21) Reference T2 (0.22 – 2.08) OR = 1.79 (1.44, 2.23) P <0.001 T3 (> 2.08)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			OR = 5.99 (4.15, 8.66) P <0.001 <u>Trend Test</u> P <0.001 • Odds (95% CI) of mild DF per 1 mg/L increase in urinary fluoride level OR = 1.56 (1.45, 1.67) P <0.001 ***Moderate DF*** • Odds (95% CI) of moderate DF per 1 mg/L increase in water fluoride level OR = 3.85 (3.01, 4.92) P <0.001 • Odds (95% CI) of moderate DF per 1	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			mg/L increase in urinary fluoride level OR = 2.85 (2.39, 3.39) P <0.001	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for major confounders such as age, gender, BMI, low birth weight, maternal education, paternal education and family income
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (children with cavities or had orthodontic appliances during the investigarion period)
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the national standardized ion selective electrode method
	Can we be confident in the outcome assessment?	++	* Yes, outcome (dental fluorosis) was measured independently by two dentists using Dean's Fluorosis Index. * Yes, outcome (mitochondrial DNA) was measured using DNA samples extracted from lymphocytes using the DNA extraction kit (GK1042, Shanghai Generay

Risk of bias assessment			
			Biotech Co., Ltd., Shanghai, China), and quantified using the Nanodrop ND1000 (Thermo scientific, Wilmington, DE, USA). * Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Bashash 2018 [71]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposures:** Fluoride levels in	**Outcomes:** • Attention-deficit/ hyperactivity disorder (ADHD) related	**Statistical analysis:** • Multivariate gamma regression models were used	Positive association between higher prenatal fluoride

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Prospective cohort study **Country:** Mexico **Participants:** Mother-child pairs residing in Mexico City enrolled in two of four cohorts of the Early Life Exposures to Environmental Toxicants (ELEMENT) study; specifically, participants from	• Maternal urinary samples (prenatal fluoride exposure biomarker) **Method of exposure assessment:** • ≥ 1 second morning void spot urine sample from gestational period was used and adjusted for creatinine • Number of participants (N) with maternal urinary fluoride measures adjusted for creatinine by trimester: <u>1st Trimester:</u> N = 175 <u>2nd Trimester:</u>	symptoms in children between 6 to 12 years of age **Method of outcome ascertainment:** <u>Conners' Rating Scales-Revised (CRS-R)</u> • Completed by mothers • Used to evaluated ADHD related behaviours • Scores the following: Cognitive Problems + Inattention, Restless-Impulsive, Hyperactivity, ADHD Index, DSM-IV Inattention, DSM-IV Hyperactivity-Impulsivity, and DSM-IV ADHD Total	• Models were adjusted for child characteristics (gestational age, birth weight, sex, parity, age at outcome assessment) and maternal characteristics (smoking history, marital status, education, socioeconomic status, and cohort) **Results:** Change (95% CI) in outcome per 0.5 mg/L unit increase in maternal urinary fluoride levels adjusted for creatinine	exposure and symptoms of inattention, but not hyperactivity or impulse control, in a large Mexican cohort of children, suggesting neurotoxicity of early-life exposure to fluoride

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
cohorts 2A and 3 were included in the analysis. **Sampling time frame:** Cohort 2A: • 1997 to 1999 Cohort 3: • 2001 to 2003 **Sample size (N):** 213 Mother-child pairs **Sex:** Girls: • N (%) = 116 (54)	N = 80 3rd Trimester: N = 62 • Number of participants (N) by number of measurements 3 measurements: N = 14 2 measurements: N = 78 1 measurement: N = 122 **Exposure levels:** • Mean (95% CI) level of fluoride in maternal	Conners' Continuous Performance Test, 2nd edition (CPT-II) • Completed by children • Used to evaluate sustained attention and inhibitor control • Scores the following: Omission Errors, Commission Errors, and Hit Reaction Time Other Details • CRS-R and CPT-II were completed during the same visit • Age and sex standardization were applied to outcome measures • Experienced psychologist oversaw the psychometric tests performed	• CRS-R scores (N = 210) Cognitive Problems + Inattention β= 2.54 (0.44, 4.63) p= 0.0178 Restless-Impulsive β= 1.92 (-0.07, 3.91) p= 0.0586 Hyperactivity β= 1.05 (-0.91, 3.00) p= 0.2953 ADHD Index β= 2.47 (0.43, 4.50) p= 0.0175 DSM-IV Inattention β= 2.84 (0.84, 4.84) p= 0.0054	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: • No gestational urine sample available • > 14 gestational weeks at recruitment • Child behavioral tests not conducted during specified time period (6 to 12 years of age) • History of psychiatric disorder(s) • Medical complications • Gestational use of alcohol/illegal drugs by the mother **Source of funding/ support:** U.S. NIH, NIEHS/EPA, and the National Institute of Public	urine adjusted for creatinine 0.85 mg/L (0.81, 0.90)		<u>DSM-IV Hyperactivity-Impulsivity</u> β= 1.69 (-0.33, 3.70) p= 0.1016 <u>DSM-IV ADHD Total</u> β= 2.38 (0.42, 4.34) p= 0.0176 • CPT-II scores (N = 210) <u>Omission Errors</u> β= 0.22 (-2.30, 2.74) p= 0.8643 <u>Commission Errors</u> β= -0.43 (-2.38, 1.51) p= 0.6641 <u>Hit Reaction Time</u> β= 1.07 (-1.19, 3.32)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Health/Ministry of Health of Mexico; facilities provided by the American British Cowdray Hospital **Author declaration of interest:** NR			p= 0.3546	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were maternal-child pairs from Mexico City, and consisted of two of four cohorts from the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) study. Time of recruitment was from 1997 to 1999 for cohort 2A and 2001 to 2003 for cohort 3; however, mean maternal urinary fluoride levels adjusted for creatinine was not significantly different between groups.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, regression models were adjusted for child characteristics (gestational age, birth weight, sex, parity, and age at outcome assessment), and maternal characteristics (smoking history, marital status, education, socioeconomic status, and cohort). Interaction between sex and maternal urinary fluoride levels adjusted for creatinine was assessed in sensitivity analysis.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment					
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable		
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	231 mothers with a minimum of one MUFcr and a matching outcome (CRS-R or CPT-II) were identified for this project. However, complete demographic and outcome information were missing among 17 mother-child pairs, leaving 214 participants for our analyses, of whom 210 mother-child pairs had data for the CRS-R and CPT-II analyses (206 had data for both) (Fig. 1).		
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in maternal urinary samples collected during pregnancy. No difference in exposure assessment methods were reported between study participants.		
	Can we be confident in the outcome assessment?	+	Participants were recruited at 14 gestational weeks or less, and outcomes were measured in children between 6	++	Participants were recruited at 14 gestational weeks or less, and outcomes were measured in children between 6 to 12 years of age; regression models

Risk of bias assessment					
			to 12 years of age; regression models were adjusted for the age at outcome assessment. Conners' Rating Scales-Revised (CRS-R) was completed by the mother. "... parents were unaware of their offspring's fluoride exposure status, removing reporting bias as a limitation. An experienced psychologist oversaw the psychometric tests. However, missing		were adjusted for the age at outcome assessment. Conners' Continuous Performance Test (CPT-II) was completed by the child. An experienced psychologist oversaw the psychometric tests.

Risk of bias assessment				
			teacher assessment report is a major limitation.	
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the methods section were reported on in the results section.	
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.	

Cui 2018 [72]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type:	**Exposure:**	**Outcomes:**	**Statistical analysis:**	• In the overall participants, the

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Original study **Study design:** Cross-sectional study **Country:** China **Participants:** Children (7 to 12 years of age) from four schools in Tianjin found in locations with historic endemic (1.52 – 2.49 mg/L fluoride level in drinking water) and non-endemic (0.20 –	Fluoride levels in urine samples **Method of exposure assessment:** • Morning urine samples were collected • Measured using ion selective electrode method **Exposure levels:** Median (interquartile range) levels of fluoride in urine by DRD2 single nucleotide polymorphism (SNP) • CC (N = 103) 1.3 (0.9 – 1.6)	• Intelligence quotient (IQ) **Method of outcome ascertainment:** • Determined using the Combined Raven's Test – The Rural in China (CRT-RC) method • Test was administered by professionals • Age-specific groups of the CRT-RC: Low: ≤ 69 Borderline: 70 – 79 Low average: 80 – 89 Average: 90 – 109 High average: 110 – 119	• Multiple linear regression models were used • Model for overall were adjusted for age of child, maternal education, smoker in the family, stress, and anger • Model for DRD2 SNP of CC or CT was adjusted for age of child, maternal education, smoker in the family, stress, and anger • Model for DRD2 SNP of TT was adjusted for age of child and having a cold • Robust estimates of variance were acquired using a bootstrap procedure **Result:**	DRD2 Taq 1A polymorphism itself was not related to IQ scores in children who had a high level of urine fluoride. • In the CC/CT subgroup, urine fluoride levels and IQ scores in children were unrelated. • Among the participants carrying the TT genotype, there was a strong and robust negative linear relationship between log-urine fluoride and IQ scores in children after adjusting for child age and have a cold more than 5 times a year.

450

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
1.00 mg/L levels of fluoride in drinking water) fluorosis. **Sampling time frame:** 2014 – 2015 **Sample size (N):** 323 **Sex:** <u>Boys:</u> • N (%) = 177 (54.8) **Exclusions:** • Informed consent forms not signed by guardians	• <u>CT (N = 179)</u> 1.2 (0.8 – 1.8) • <u>TT (N = 44)</u> 1.3 (1.0 – 2.0)	Good: 120 – 129 Excellent: ≥ 30	• Change (95% CI) in IQ score per log-unit increase in urinary fluoride among all participants and by subgroups <u>Overall (N = 323)</u> β = -2.47 (-4.93, -0.01) p = 0.049 [Bootstrapped estimate: 95%CI = -4.97, 0.03; p = 0.053] <u>DRD2 SNP of CC or CT (N = 279)</u> β = - 1.59 (- 4.24, 1.05) p = 0.236 [Bootstrapped estimate:	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Moved • No measurement of dopamine receptor-2 (DRD2) genotyping **Source of funding/ support:** • National Nature Science Foundation of China • Scientific and Technological Project of Tianjin Medicine in 2014 • Scientific and Technological Project of Tianjin Centers for Disease Control and Prevention **Author declaration of interest:** None			95%CI = -4.14, 0.95; p = 0.220] <u>DRD2 SNP of TT (N = 44)</u> β = -12.31 (-18.69, -5.94) p = < 0.001 [Bootstrapped estimate: 95%CI = -19.66, -4.96; p = 0.001] • "…the safety threshold of urine fluoride levels in the subgroup TT was 1.73 mg/L (95% CI = (1.51	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			mg/L, 1.97 mg/L))" (p. 276)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were children (7 to 12 years of age) from four schools in Tianjin (2014-2015) found in locations with historical endemic (1.52 - 2.49 mg/L fluoride level in drinking water) and non-endemic (0.20 - 1.00 mg/L levels of fluoride in drinking water) fluorosis.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Model for overall was adjusted for age of child, maternal education, smoker in the family, stress, and anger. Model for DRD2 SNP of CC or CT was

Risk of bias assessment			
			adjusted for age of child, maternal education, smoker in the family, stress, and anger. Model for DRD2 SNP of TT was adjusted for age of child and having a cold.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided. A total of 400 children (7–12 years old) were enrolled. Children who had no informed consent form signed by their guardians or moved out (n = 35) and no DRD2 genotyping measurement (n = 42) were excluded, leaving 323 children for the study.
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in urine. No differences in exposure assessment methods were reported between participants.
	Can we be confident in the outcome assessment?	++	The Combined Raven's Test - The Rural in China (CRT-RC) method was used by professionals to

Risk of bias assessment			
			determine child IQ. Outcome unlikely to be affected by blinding status.
Selective reporting	Were all measured outcomes reported?	++	The outcome mentioned in the study objective was reported on in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Jimenez-Cordova 2018 [73]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study	**Exposures:** <u>Fluoride levels in</u> • Drinking water samples • Urine samples	**Outcomes:** <u>Kidney injury</u> • Urine levels of albumin (ALB), cystatin-C (Cys-C), kidney injury	**Statistical analysis:** • Multiple linear regression analysis was used • Interaction analysis between fluoride and tAS was conducted	• "…urinary excretion of 4 early kidney injury biomarkers (ALB, Cys-C, KIM-1 and OPN) is related to environmental F exposure in an adult population, without an As interaction effect.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Mexico **Participants:** Adult (18 to 77 years of age) residents of 3 Chihuahua communities (El Sauz, Aldama, and Gpe. Victoria) exposed to fluoride via drinking water **Sampling time frame:** July 2013 **Sample size (N):** 239	**Co-exposure:** Arsenic levels in • Urine samples **Method of exposure assessment:** Fluoride levels in water and urine samples • Potentiometric method using ion selective electrode Inorganic arsenic and corresponding metabolite levels in urine samples • Hydride generation-cryotrapping-atomic absorption spectrometry using Perkin Elmer Analyst	molecule 1 (KIM-1), clusterin (CLU), osteopontin (OPN), and trefoil factor 3 (TIFF-3)) Kidney function • Glomerular filtration rate (eGFR) **Method of outcome ascertainment:** eGFR • Estimated using levels of creatinine (Creat) in serum and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula • Commercial kit used to determine Creat levels in urine	• Results considered significant at $p < 0.05$ and marginally significant at $p < 0.1$ • ALB models were adjusted for specific gravity, protein (15 mg/dL), protein (30 mg/dL), mine-worker, Diabetes, urine leucocytes, Age, sex • Cys-C models were adjusted for specific gravit, protein (15 mg/dL), protein (30 mg/dL) amorphous urate crystals, and age • OPN models were adjusted for specific gravity, amorphous urate crystals, age, and sex • CLU models were adjusted for specific gravity, protein (15 mg/dL), protein (30 mg/dL), smoking index, age, and sex	Our results suggest a possible tubular dysfunction from F exposure that might increase susceptibility to the future development of CKD." (p. 104)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: Men • N (%) = 68 (28.8) **Exclusions:** • < 18 years of age • Infrequent consumption of tap water • Live in study area for < 1 year • Have cancer or kidney disease **Source of funding/ support:** Mexican National Council of Science and Technology	400 spectrometer and multi-atomizer • Total urinary arsenic (tAS) is the sum of inorganic arsenic and corresponding metabolites monomethylarsonic acid (MAs) or dimethylarsinic acid (DMAs) Normalization of fluoride and tAS levels in urine • Levine-Fahy method and urinary strip specific gravity **Exposure levels:** • Geometric mean (Interquartile range; IQR) level of water fluoride (mg/L); N = 232	Urinary kidney damage biomarkers • First morning void samples used • Luminex xMAP Technology using MILLIPLEX MAP Human Kidney Toxicity panel 3 and 4 • Biomarker levels in urine were adjusted for specific gravity and Creatinine	• KIM-1 models were adjusted for specific gravity, amorphous urate crystals, mucoprotein, atherogenic index, and age • TFF-3 models were adjusted for specific gravity, diabetes, age, and sex • eGFR models were adjusted for vascular diseases, cholesterol, alkaline phosphatase, and nephrotoxic drug use **Results:** • Change in outcome (p-value) per unit increase of fluoride in water (mg/L) and urine (µg/mL) ALB (µg/mL)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: None	1.5 (0.19 – 1.8) • Geometric mean (IQR) level of urinary fluoride (µg/mL); N = 236 2.0 (1.1 – 3.5) • Geometric mean (IQR) level of urinary tAS (ng/mL); N = 236 18.55 (10.6 – 34.1) • Geometric mean (IQR) level of urinary inorganic As (ng/mL); N = 236 1.8 (0.91 – 4.4)		Water: β= 1.20 (p= <0.001) Urine: β= 0.56 (p= <0.001) <u>Cys-C (µg/mL)</u> Water: β= 0.03 (p= 0.005) Urine: β= 0.022 (p= 0.001) <u>OPN (µg/mL)</u> Water: β= 0.10 (p= 0.028) Urine: β= 0.038 (p= 0.041) <u>CLU (µg/mL)</u> Water: β= 0.09 (p= 0.118)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Urine: β= 0.07 (p= 0.100) <u>KIM-1 (ng/mL)</u> Water: β= 0.045 (p= 0.162) Urine: β= 0.048 (p= 0.008) <u>TFF-3 (ng/mL)</u> Water: β= 2.88 (p= 0.010) Urine: β= 1.14 (p= 0.115) <u>eGFR (mL/min/1.73 m^2)</u> Water: β= 0.19 (p= 0.675) Urine: β= 0.49 (p= 0.030)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants consisted of adult residents of 3 Chihuahua communities in Mexico. The study was conducted in July 2013.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Multiple linear regression models were adjusted for several confounders. List of confounders vary by outcome. See Table 4 on p. 102 for details. Arsenic was assessed for potential interaction with fluoride.

Risk of bias assessment			
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided for the study. "Adults who reported cancer or kidney disease were excluded from the study." (p. 98) Three participants without samples of urine were excluded.
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in water and urine. No difference in exposure assessment methods were found between study participants.
	Can we be confident in the outcome assessment?	++	Kidney injury biomarkers were measured in urine, and eGFR was estimated using levels of creatinine in serum and the Chronic Kidney Disease Epidemiology Collaboration formula. Blinding status unlikely to affect outcome assessment.
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the abstract were reported on in the results section.

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Kumar, V 2018 [74]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** India	**Exposures:** <u>Fluoride levels in</u> • water • Serum • Urine **Method of exposure assessment:** • Manual titration method, automatic	**Outcomes:** <u>Thyroid functional activity</u> • Serum levels of free triiodothyronine (T3), free thyroxine (T4), and thyroid stimulating hormone (TSH)	**Statistical analysis:** • Chi-square and Mann Whitney tests • Results considered significant at p<0.05 **Results:** • Mean free T3 (pg/ml) by study group A: 3.125; B: 2.698	• Mean TSH, water fluoride levels, urine fluoride levels and serum fluoride levels of subjects of group 1 were found to be significantly higher than that of subjects of group 2 (p-value < 0.05). • Fluorosis and thyroid functional activity are positively correlated with each other.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Children (8 to 15 years of age) from endemic fluorosis area and fluorosis non-endemic area **Sampling time frame:** NR **Sample size (N):** 400 <u>Group A (N = 200):</u> Subjects from endemic fluorosis area • A1 (N = 100): Subjects with dental fluorosis	analyzer, and radiometer **Exposure levels:** • Mean (range) level of water fluoride (ppm) by study groups A1: 1.1 (1.5 – 5) A2: 3.3 (1.8 – 5.8) B: 0.99 (0.94 – 1.08) • Range of urinary fluoride (ppm) level by study groups A1: 0.27 – 8.6 A2: 0.6 – 7.64 B: 0.22 – 1.07 • Range of serum fluoride (ppm) level by study groups A1: 0.05 – 0.71 A2: 0.05 – 0.71 B: 0.03 – 0.10	**Method of outcome ascertainment:** • Immuno Chemiluminescence Mircroparticle Assay with Autoanalyzer	p = 0.26 • Mean free T4 (ng/dL) by study group A: 1.282; B: 1.193 p = 0.41 • Mean TSH (µlU/m) by study group A: 3.849; B: 2.588 p = 0.02 • Mean water fluoride (ppm) by study group A: 2.877; B: 1.020 p = 0.01 • Mean urinary fluoride (ppm) by study group A: 2.982; B: 0.761 p = 0.02 • Mean serum fluoride (ppm) by study group A: 0.195; B: 0.059 p = 0.03 • Percent (%) of thyroid hormone level	• Excessive fluoride levels also lead to alteration in thyroid hormones activity

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• A2 (N = 100): Subjects with no dental fluorosis <u>Group B (N = 200):</u> Subjects from fluorosis non-endemic area (controls) • Subjects with no dental fluorosis **Sex:** NR **Exclusions:** • ≥ 15 years of age • History of cancer, chronic disease, other type of dental staining, and medication use that interferes with thyroid			derangement by study group A: 67.5; B: 54	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding/ support: None **Author declaration of interest:** None				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants consisted of children 8 to 15 years of age. Information on recruitment time frame and participation rate not found.

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Subjects more than 15 years of age, or having history of the presence of any other form of dental staining, cancer/chronic disease and having thyroid-interfering medication were excluded from the study. Sample sizes were the same between study groups.
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in water, urine, and serum. No differences in exposure assessment methods were found between study groups.
	Can we be confident in the outcome assessment?	++	Thyroid hormones were measured in serum, and therefore are unlikely to be affected by blinding status.
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the introduction section were reported on in the results section.

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Kumar, S 2018 [75]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:**	**Exposures:** Fluoride levels in • Water samples **Method of exposure assessment:** • Electrochemical probe method IS-3025 (Part 60).	**Outcome(s):** Severity of Dental Fluorosis (DF) **Method of outcome ascertainment:** • DF severity was determined using the Modified Dean Index	**Statistical analysis:** • Logistic regression analysis conducted to examine association between DF and potential risk factors • Model variables include location, water storage method, and water fluoride content • Statistical significance at $p < 0.05$	"The severity of dental fluorosis is positively correlated with the fluoride content in the water. The water fluoride content is the strongest predictor

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
India **Participants:** Adolescents (12 to 15 years of age) from 16 schools in Jhabua and Dhar districts **Sampling time frame:** January 2015 to July 2015 **Sample size:** 800 **Sex N (%):**	**Exposure level:** <u>Mean (SD) water fluoride levels</u> • Jhabua: 1.29 (±0.52) • Dhar: 1.23 (±0.39) • Total: 1.27 (±0.46)	• Examinations were conducted by trained dentists • Instruments included mouth mirror and community periodontal index probe	**Results:** <u>Correlation between water fluoride levels (ppm) and DF severity</u> • r = 0.967; p = 0.000 <u>Odds (95% CI) of DF at >1.2ppm compared to ≤ 1.2ppm</u> • OR = 1.764 (1.309, 2.377); p < 0.0001	for dental fluorosis.” (p. 6)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Boys: 398 (49.75%) **Exclusions:** • Medically compromised • Unwilling to participate • No parental consent **Source of funding / support:** None that would influence the results **Author declaration of interest:** No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it considered for major confounders such as sex, residency, storage of water, dental hygiene, diet
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (unwilling to participate, medically compromised, or whose parents did not give consent)

Risk of bias assessment					
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the electrochemical probe method IS-3025 (Part 60).		
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was done by trained dentists, using Dean's modified index. Lack of blinding of outcome assessors would not appreciably bias results.	++	Yes, outcome (mitochondrial DNA) was measured using DNA samples extracted from lymphocytes using the DNA extraction kit (GK1042, Shanghai Generay Biotech Co., Ltd., Shanghai, China), and quantified using the Nanodrop ND1000 (Thermo scientific, Wilmington, DE, USA). Lack of blinding of outcome

Risk of bias assessment					
					assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction		
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified		

Malin 2018 [76]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposures** Fluoride levels in • Drinking water	**Outcome(s)** Thyroid function	**Statistical analysis:** • Linear regression was used to model TSH	"Adults living in Canada who have moderate-to-severe

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Cross-sectional study **Country**: Canada **Sampling period** Cycle 3 (2012 – 2013) **Participants:** North Americans (3-79) from 16 cities (CHMS) **Sample size:** 6,914,124 **Sex (%):** Men: 51.54%	• Urine <u>Iodine level in</u> • Urine **Method of exposure ascertainment** <u>Water fluoride</u> Basic anion exchange chromatography. <u>Urinary fluoride</u> Non-fasting spot samples, analyzed using an Orion PH meter with a fluoride ion selective electrode after being diluted with an ionic adjustment buffer	**Method of outcome ascertainment** Serum TSH	levels as a function of urinary fluoride and iodine levels • Adjusting for age, sex BMI, serum calcium) **Results** <u>Water fluoride (mg/L)</u> Mean ±SD: 0.22 ±0.24 <u>Urinary fluoride (mg/L)</u> Mean ±SD: 0.94 ±1.05 ***Change (95%CI) in serum TSH (mIU/L) per unit increase in UFsg (mg/L)*** <u>No iodine deficiency</u> *ß = -0.02 (-0.19, 0.15)*	iodine deficiencies and higher levels of urinary fluoride may be at an increased risk for underactive thyroid gland activity.”

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: • People living in the 3 territories, remote areas, reserves, or aboriginal settlements, full-time North American military, and institutionalized persons • Use of thyroid drugs • Prior thyroid disease**s** • Pregnancy with excess iodine levels (> 2.37 µmol/L) **Source of funding:** • SSHRC • CIHR • CFI • Statistics Canada **Conflict of interest:** No COI	<u>Iodine</u> Colorimetric microplate assay (using spot urine samples) **Water fluoride** 0.22 mg/L ± 0.24 **Urinary fluoride** 0.94 mg/L ± 1.05		*p = 0.43* <u>Iodine deficiency</u> *ß = 0.36 (-0.03, 0.75)* *p = 0.03*	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Were the comparison groups appropriate?	**++**	Participants 3-79 years old were recruited from 16 sites across all provinces from Cycle 3 (2012–2013) of the CHMS. Exclusions included: people living in the 3 territories, on reserves or other aboriginal settlements in the provinces, full-time members of the North American forces, institutionalized people, and those living in remote areas, pregnant women, those with thyroid conditions or abnormally high iodine levels. The overall response rate for all aspects of Cycle 3 was 79%
Confounding	Did the study design or analysis account for important confounding and modifying variables?	**++**	Yes (sex, age, BMI, total household income, serum calcium level, specific gravity of urinary fluoride concentration)

Risk of bias assessment			
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Missing data were<5% in all analyses except for household income which was reported by 77% of respondents; however, Statistics Canada provided imputed estimates for these missing values.
Detection	Can we be confident in the exposure characterization?	++	Yes, urinary fluoride was measured in non-fasting spot samples, adjusted for specific gravity (UFSG), and analyzed using an Orion PH meter with a fluoride ion selective electrode after being diluted with an ionic adjustment buffer. Samples were not standardized though with respect to collection time.
	Can we be confident in the outcome assessment?	++	TSH was measured in blood samples collected by a phlebotomist using a standard venipuncture method. Serum TSH was measured using a 3rd generation assay analyzer equipped with a chemiluminescent detection system. Serum free T4 was analyzed using a competitive chemiluminescent

Risk of bias assessment			
			immunoassay. Thyroid hormones were analyzed at the INSPQ on the Siemens ADVIA Centaur XP analyzer. Iodine level was measured in spot urine samples by colorimetric microplate assay.
Selective reporting	Were all measured outcomes reported?	**++**	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	**++**	None identified

Mohd Nor 2018 [77]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposures:**	**Outcome(s):** Dental fluorosis	**Statistical analysis:**	"Findings indicate that the change in

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Cross sectional **Country:** Malaysia **Participants:** Lifelong residents aged 9- and 12-year-olds **Sampling time frame:** 2015 (calculated using the following information reported by the authors) • 9-year-old children (born between 1 January and 31 December 2006	Fluoride levels in public drinking water supply **Method of exposure assessment:** Water fluoride: NR **Exposure level:** • Original: 0.7 ppm • Reduced: 0.5 ppm	**Method of outcome ascertainment:** • Assessment of dental fluorosis was conducted by trained clinical and calibrated examiners (NAMN). • Assessment of fluorosis was conducted by examining the maxillary central incisors using Dean's Fluorosis Index. • Consensus on outcome assessment must be achieved by agreement of two additional examiners, who did not participate in children's examination, with the initial examiner.	• Binary logistic regression **Results:** • "The prevalence of fluorosis (Dean's score ≥ 2) among children in the fluoridated area (35.7%, 95% CI: 31.9%-39.6%) was significantly higher (P < 0.001) than children in the nonfluoridated area (5.5%, 95% CI: 3.6%-7.4%)." • "Of those in the fluoridated area, the prevalence of fluorosis decreased from 38.4% (95% CI: 33.1% 44.3%) for 12-year-olds to 31.9% (95% CI: 27.6%-38.2%) for 9-year-olds, although this difference was not statistically significant (P = 0.139)."	fluoride level from 0.7 to 0.5 ppm has reduced fluorosis and maintains a caries-preventive effect. Although there is a reduction in fluorosis prevalence, the difference was not statistically significant."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• 12-year-old children (born between 1 January and 31 December 2003) **Sample size:** 1,143 children aged 9-12 years old **Sex:** Boys: 491 (43%) **Exclusions:** • Children who missed clinical examination. • Children with unerupted, partially unerupted or fractured incisor(s), or have a fixed orthodontic appliance.			**Fluorosis prevalence no. (%)** <u>(0) Normal</u> • Fluoridated: 342 (56.3) • Nonfluoridated: 494 (90.1) <u>(1) Questionable</u> • Fluoridated: 41 (6.8) • Nonfluoridated: 23 (4.2) <u>(2) Very mild</u> • Fluoridated:95 (15.7) • Nonfluoridated: 23 (4.2) <u>(3) Mild</u> • Fluoridated: 65 (10.7) • Nonfluoridated: 5 (0.9) <u>(4) Moderate</u> • Fluoridated:53 (8.7) • Nonfluoridated: 2 (0.4)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding / support: Ministry of Higher Education, Malaysia **Author declaration of interest:** No COI			<u>(5) Severe</u> • Fluoridated:0 • Nonfluoridated: 0 <u>Not able to score</u> • Fluoridated:11 (1.8) • Nonfluoridated: 1 (0.2) <u>Total</u> • Fluoridated:607 (100.0) • Nonfluoridated: 548 (100.0) <u>Fluorosis (Deans > 0)</u> Fluoridated: 254 (42.6), *P<0.001* Nonfluoridated: 53 (9.7) <u>Fluorosis (Deans ≥ 2)</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Fluoridated:213 (35.7), *P<0.001* Nonfluoridated: 30 (5.5) **Bivariate analysis of fluorosis prevalence with different fluoride exposures** <u>Fluorosis Deans ≥2</u> *0 ppm lifetime* • N (%): 30 (12.30%) • OR (95% CI), p-value: Ref. *0.5 ppm lifetime* • N (%): 100 (41.2%) • OR (95% CI), p-value: 8.45 (5.45-13.10), 0.001	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			0.7 ppm for first 2 years *and then 0.5 ppm* • N (%): 113 (46.5%) • OR (95% CI), p-value: 10.88 (7.03-16.84), 0.001 <u>Any fluorosis: Deans > 0</u> *0 ppm lifetime* • N (%): 53 (9.7%) • OR (95% CI), p-value: Ref. *0.5 ppm lifetime* • N (%): 123 (40.5%) • OR (95% CI), p-value: 6.33 (4.40-9.12), 0.001 *0.7 ppm for first 2 years* *and then 0.5 ppm* • N (%): 161 (55.1%) • OR (95% CI), p-value: 7.58 (5.26-10.93), 0.001	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Fluorosis prevalence after fluoride concentration in the water supply was reduced <u>Fluorosis (Deans > 0)</u> *% Prevalence 12-year-old (PreReduction)* • Fluoridated: 44.6 • Nonfluoridated (control): 10.3 *% Prevalence 9-year-old (PostReduction)* • Fluoridated: 39.3 • Nonfluoridated (control): 8.9 *% Difference (post-pre)*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Fluoridated: −5.3 • Nonfluoridated (control): −1.4 *% Difference (pre)* • Fluoridated: 34.3 *% Difference (post)* • Fluoridated: 30.4 <u>Fluorosis (Deans ≥ 2)</u> *% Prevalence 12-year-old (PreReduction)* • Fluoridated: 38.4 • Nonfluoridated (control): 4.7 *% Prevalence 9-year-old (PostReduction)* • Fluoridated: 31.9 • Nonfluoridated (control): 6.5	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			% Difference (post-pre) • Fluoridated: −6.5 • Nonfluoridated (control): 1.8 *% Difference (pre)* • Fluoridated: 33.7 *% Difference (post)* • Fluoridated: 25.4	

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable
	Was allocation to study groups adequately concealed?	N/A Not applicable

Risk of bias assessment			
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (children who missed clinical examination, or children with unerupted, partially unerupted or fractured incisor(s), or have a fixed orthodontic appliance).
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from public water supply records
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured using the Dean's Index by 1 clinical examiner and verified by 2 trained examiners who were not involved in the clinical examination. The diagnosis of dental fluorosis was

Risk of bias assessment			
			confirmed only based on agreement of three out of four dentists of each group agreed. conditions. All examiners were blinded to the exposure status, with unique coding of each photograph.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Mustafa 2018 [78]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type:	**Exposure:**	**Outcomes:**	**Statistical analysis:**	• Life-long fluoride intake from combined sources for

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Original study **Study design:** Ecological study **Country:** Sudan **Participants:** primary school students (6 to 14 years of age) residents of rural areas in Khartoum state **Sampling time frame:** NR	<u>Fluoride levels in</u> • Groundwater samples **Method of exposure assessment:** • Rainy and dry season samples were acquired from rural parts of Khartoum state • A sample of 16 groundwater wells were collected per season • Analyzed "using SPADNS reagent as described by Standard Methods." (p. 105) **Exposure levels:** • Range for levels of fluoride in	• Schooling performance (average score and high score [> 70%] prevalence) **Method of outcome ascertainment:** <u>Subjects assessed</u> • Islamic studies I • Islamic studies II • Arabic • English • Mathematics • Sciences • History • Technology <u>Primary examination results</u> • Acquired from the Ministry of Education-Khartoum State	• Pearson correlation analysis was conducted **Results:** **Ground water fluoride** <u>*Dry season*</u> *0.14 – 2.07 mg/L* <u>*Rainy season*</u> *0.01 – 1.34 mg/L* • Correlation between average level of fluoride in drinking water (mg/L) and average school performance score (%) by subject <u>Islamic studies I</u>	adolescents in the United States were not strongly associated with pQCT bone measures at age 17. • Findings provide support to the assertion that fluoride intakes, within these ranges, are not associated with adverse consequences on bone outcome measures by age 17.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size (N): N = 775 **Sex:** • Boys N = 315 **Exclusions:** NR **Source of funding/ support:** • Primary school results from the Ministry of Education-Khartoum State • Financial support from the Department of Research, Ministry of Higher Education and Scientific Research, Sudan	groundwater by season <u>Dry season</u> 0.14 – 2.07 mg/L <u>Rainy season</u> 0.01 – 1.34 mg/L	• Obtained for schools in locations sampled for groundwater	r = -0.50; p = 0.008 <u>Islamic studies II</u> r = -0.47; p = 0.013 <u>Arabic</u> r = -0.32; p = 0.11 <u>English</u> r = -0.46; p = 0.016 <u>Mathematics</u> r = - 0.33; p = 0.097 <u>Sciences</u> r = -0.53; p = 0.005 <u>History</u> r = -0.59; p = 0.001 <u>Technology</u> r = -0.30; p = 0.158	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: NR			Overall score r = -0.51; p = 0.007 • Correlation between average level of fluoride in drinking water (mg/L) and the prevalence of high school performance score (%) by subject Islamic studies I r = -0.59; p = 0.001 Islamic studies II r = -0.35; p = 0.078 Arabic r = -0.47; p = 0.014 English r = -0.41; p = 0.034 Mathematics r = -0.39; p = 0.045 Sciences	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			r = -0.60; p = 0.001 History r = -0.46; p = 0.016 Technology r = -0.22; p = 0.265 Overall score r = -0.48; p = 0.012	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants consisted of children (6 to 14 years of age) in primary school who resided in rural areas of

Risk of bias assessment			
			Khartoum state. The recruitment timeframe was not found.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	No mention of excluding participants or missing data.
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in groundwater. No difference in exposure assessment methods was found between study areas.
	Can we be confident in the outcome assessment?	++	Primary examination results provided by the Ministry of Education-Khartoum State were used to determine school performance. "The examinations are set and organized by the educational authorities of each state"

Risk of bias assessment			
			(p. 105). Outcome unlikely to be affected by blinding status.
Selective reporting	Were all measured outcomes reported?	++	Outcomes mentioned in the abstract were also reported on in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	+	Exposure was assessed at each study area. As individual levels of exposure were not measured, the possible variation between participants within a study area could not be accounted for in the analysis (i.e. the potential exposure difference between those who drink more water than those who drink less water).

Oweis 2018 [79]

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study	**Exposure:**	**Outcomes:**	**Statistical analysis:**	• "In summary, the findings show that the effects of life-long fluoride intake from

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Study design: Prospective cohort study **Country:** USA **Participants:** Adolescents (17 years of age) whose families were recruited into the Iowa Fluoride Study (IFS) from hospitals following birth **Sampling time frame:**	<u>Period-specific daily intake of fluoride</u> • Birth to 8.5 years • 8.5 to 14 years • 14 to 17 years • Birth to 17 years <u>Cumulative average daily intake of fluoride</u> • Birth to 17 years **Method of exposure assessment:** • Questionnaires were administered to determine fluoride intake frequency and amounts, and were distributed at the following time periods: " ages 1.5, 3, 6, and 9 months, then every four months up to age 4 years, and	<u>Radial and tibial bone characteristics</u> • Cortical content • Cortical density • Trabecular content • Trabecular density • Compression strength • Torsion strength **Method of outcome ascertainment:** • Peripheral quantitative computed tomography (pQCT) used to acquire measurements at 17 years of age • The total compression strength of the bone was calculated using the total area and total density • Radiographic imaging was performed by	• Multivariate regression models were used • Models were adjusted for height, weight, calcium and protein intake, time since peak height velocity (PHV), and physical activity. • Results were considered significant at $p < 0.01$ • Results were considered suggestive at $0.01<p<0.05$ **Results:** **RADIAL BONE - GIRLS** • Change (SE) in trabecular content (mg) per 1 mg unit increase in daily	combined sources for adolescents in the United States were not strongly associated with pQCT bone measures at age 17... the study findings provide support to the assertion that fluoride intakes, within these ranges, are not associated with adverse consequences on bone outcome measures by age 17." (p. 9)

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
IFS: 1992 to 1995 Iowa Bone Development Study (IBDS) – IFS Subset 1998 to 2000 **Sample size (N):** 380 **Sex (N):** • Boys N = 176 **Exclusions:** NR **Source of funding/ support:**	then every 6 months up to age 17 years." (p. 5) • Sources of exposure assessed include "… water, other beverages, selected foods, dietary fluoride supplements, and ingested fluoride toothpaste …" (p. 4) • Assays of individual and filtered water, select foods, and beverages were performed to determine the amount of fluoride • State health department records were used to determine levels of fluoride in public water **Exposure levels:**	technicians (N = 2) who were certified with the International Society of Clinical Densitometry (ISCD) • "The non-weight bearing, non-dominant arm, and the weight-bearing left leg were selected for imaging." (p. 4)	fluoride intake during the specified time period among girls 0 to 8.5 years (N = 140) β = -2.60 (2.53) p = 0.31 8.5 to 14 years (N = 125) β = -0.15 (2.21) p = 0.95 14 to 17 years (N = 122) β = 0.09 (1.84) p = 0.96 0 to 17 years (N = 112) β = 0.59 (3.30) p = 0.86	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• NIH grants • Wright-Bush Shreves Endowed Professor Fund • University of Iowa **Author declaration of interest:** NR	• Range for level of fluoride intake Women: 0.7 - 0.8 mg /day Men: 0.7 - 0.9 mg /day.		• Change (SE) in trabecular density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among girls 0 to 8.5 years (N = 140) β = 2.22 (9.50) p = 0.82 8.5 to 14 years (N = 125) β = -3.79 (8.08) p = 0.64 14 to 17 years (N = 122) β = 3.70 (6.59) p = 0.58 0 to 17 years (N = 112)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 0.99 (12.14) p = 0.94 • Change (SE) in cortical content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among girls <u>0 to 8.5 years (N = 140)</u> β = -5.79 (2.54) p = 0.03 <u>8.5 to 14 years (N = 125)</u> β = -0.74 (2.19) p = 0.74 <u>14 to 17 years (N = 122)</u> β = -1.19 (1.76) p = 0.50	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			0 to 17 years (N = 112) β = -3.19 (3.33) p = 0.34 • Change (SE) in cortical density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among girls 0 to 8.5 years (N = 140) β = 5.30 (4.44) p = 0.24 8.5 to 14 years (N = 125) β = -4.30 (3.63) p = 0.24 14 to 17 years (N = 122)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 0.42 (3.05) p = 0.89 <u>0 to 17 years (N = 112)</u> β = -2.28 (5.46) p = 0.68 • Change (SE) in compression strength (mg^2/mm^4) per 1 mg unit increase in daily fluoride intake during the specified time period among girls <u>0 to 8.5 year (N = 140)</u> β = -1.08 (2.42) p = 0.66 <u>8.5 to 14 year (N = 125)</u> β = -1.21 (2.12) p = 0.57	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			<u>14 to 17 years (N = 122)</u> β = 0.09 (1.76) p = 0.96 <u>0 to 17 years (N = 112)</u> β = -2.00 (3.10) p = 0.52 • Change (SE) in torsion strength (mm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among girls <u>0 to 8.5 years (N = 140)</u> β = -31.42 (12.28) p = 0.02 <u>8.5 to 14 years (N = 125)</u>	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = -3.76 (9.95) p = 0.71 <u>14 to 17 years (N = 122)</u> β = -7.34 (7.73) p 0.35 <u>0 to 17 years (N = 112)</u> β =-21.00 (14.95) p = 0.17 **RADIAL BONE - BOYS** • Change (SE) in trabecular content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among boys	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			<u>0 to 8.5 years (N = 125)</u> β = -4.83 (3.85) p = 0.21 <u>8.5 to 14 years (N = 112)</u> β = -1.79 (3.52) p = 0.61 <u>14 to 17 years (N = 115)</u> β = 1.41 (2.57) p = 0.59 <u>0 to 17 years (N = 105)</u> β =-5.63 (4.28) p = 0.19 • Change (SE) in trabecular density (mg/cm^3) per 1 mg unit increase in daily	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			fluoride intake during the specified time period among boys <u>0 to 8.5 years (N = 125)</u> β = 0.36 (10.77) p = 0.98 <u>8.5 to 14 years (N = 112)</u> β = -3.36 (9.22) p = 0.72 <u>14 to 17 years (N = 115)</u> β = 1.27 (7.00) p = 0.86 <u>0 to 17 years (N = 105)</u> β = -7.88 (11.51) p = 0.50	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Change (SE) in cortical content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among boys 0 to 8.5 years (N = 125) β = 2.94 (4.04) p = 0.47 8.5 to 14 years (N = 112) β = -0.36 (3.49) p = 0.92 14 to 17 years (N = 115) β = 1.82 (2.63) p = 0.49 0 to 17 years (N = 105)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 0.37 (4.10) p = 0.93 • Change (SE) in cortical density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among boys 0 to 8.5 years (N = 125) β = 11.64 (6.09) p = 0.06 8.5 to 14 years (N = 112) β = 0.92 (4.94) p = 0.86 14 to 17 years (N = 115) β = -0.51 (3.73) p = 0.90	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			0 to 17 years (N = 105) β = -0.21 (6.16) p = 0.98 • Change (SE) in compression strength (mg^2/mm^4) per 1 mg unit increase in daily fluoride intake during the specified time period among boys 0 to 8.5 years (N = 125) β = 2.70 (4.29) p = 0.53 8.5 to 14 years (N = 112) β = -0.79 (3.65) p = 0.83 14 to 17 years (N = 115)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 1.83 (2.80) p = 0.52 <u>0 to 17 years (105)</u> β = 0.72 (4.43) p = 0.88 • Change (SE) in torsion strength (mm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among boys <u>0 to 8.5 years (N = 125)</u> β = -1.08 (19.57) p = 0.96 <u>8.5 to 14 years (N = 112)</u> β = -2.02 (16.68) p = 0.91	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			14 to 17 years (N = 115) β = 14.60 (12.40) p = 0.24 0 to 17 years (N = 105) β = 8.05 (19.62) p = 0.69 **TIBIAL BONE - GIRLS** • Change (SE) in trabecular content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among girls 0 to 8.5 years (N = 136) β = 2.77 (7.78)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			p = 0.73 <u>8.5 to 14 years (N = 121)</u> β = 2.86 (6.37) p = 0.66 <u>14 to 17 years (N = 119)</u> β = -0.25 (5.60) p = 0.97 <u>0 to 17 years (N = 109)</u> β = 0.24 (10.07) p = 0.98 • Change (SE) in trabecular density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among girls	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			<u>0 to 8.5 years (N = 136)</u> β = 0.38 (9.28) p = 0.97 <u>8.5 to 14 years (N = 121)</u> β = -1.97 (7.70) p = 0.80 <u>14 to 17 years (N = 119)</u> β = 1.24 (6.10) p = 0.84 <u>0 to 17 years (N = 109)</u> β = -8.66 (11.63) p = 0.46 • Change (SE) in cortical content (mg) per 1 mg unit increase in daily	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			fluoride intake during the specified time period among girls <u>0 to 8.5 years (N = 136)</u> β = -11.97 (9.97) p = 0.23 <u>8.5 to 14 years (N = 121)</u> β = 14.18 (8.01) p = 0.08 <u>14 to 17 years (N = 119)</u> β = 11.49 (6.25) p = 0.07 <u>0 to 17 years (N = 109)</u> β = 14.24 (11.95) p = 0.24	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Change (SE) in cortical density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among girls 0 to 8.5 years (N = 136) β = 6.44 (4.91) p = 0.19 8.5 to 14 years (N = 121) β = -6.64 (3.84) p = 0.09 14 to 17 years (N = 119) β = -1.11 (3.10) p = 0.72 0 to 17 years (N = 109)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = -0.86 (6.07) p = 0.89 • Change (SE) in compression strength (mg^2/mm^4) per 1 mg unit increase in daily fluoride intake during the specified time period among girls <u>0 to 8.5 years (N = 136)</u> β = -5.39 (5.56) p = 0.34 <u>8.5 to 14 years (N = 121)</u> β = 0.96 (4.67) p = 0.84 <u>14 to 17 years (N = 119)</u> β = 3.17 (3.72) p = 0.40	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			0 to 17 years (N = 109) β = -1.62 (6.82) p = 0.82 • Change (SE) in torsion strength (mm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among girls 0 to 8.5 years (N = 136) β = -111.79 (60.22) p = 0.07 8.5 to 14 years (N = 121) β = 111.99 (49.32) p = 0.03 14 to 17 years (N = 119)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 44.73 (38.60) p = 0.25 <u>0 to 17 years (N = 109)</u> β = 64.15 (74.10) p = 0.39 **TIBIAL BONE - BOYS** • Change (SE) in trabecular content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among boys <u>0 to 8.5 years (N = 124)</u> β = -1.95 (9.08) p = 0.84	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			8.5 to 14 years (N = 111) β = 0.02 (7.82) p = 0.99 14 to 17 years (N = 114) β = 9.77 (5.84) p = 0.10 0 to 17 years (N = 104) β = -5.82 (9.37) p = 0.54 • Change (SE) in trabecular density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among boys 0 to 8.5 years (N = 124)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 9.91 (9.63) p = 0.31 <u>8.5 to 14 years (N = 111)</u> β = 2.65 (8.43) p = 0.76 <u>14 to 17 years (N = 114)</u> β = 6.64 (6.32) p = 0.30 <u>0 to 17 years (N = 104)</u> β = 7.31 (10.37) p = 0.49 • Change (SE) in cortical content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among boys	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			0 to 8.5 years (N = 124) β = 13.74 (13.05) p = 0.30 8.5 to 14 years (N = 111) β = 13.18 (11.40) p = 0.25 14 to 17 years (N = 114) β = 21.40 (8.38) p = <0.01 0 to 17 years (N = 104) β = 16.19 (13.63) p = 0.24 • Change (SE) in cortical density (mg/cm^3) per 1 mg unit increase in daily	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			fluoride intake during the specified time period among boys <u>0 to 8.5 years (N = 124)</u> β = 7.37 (5.50) p = 0.19 <u>8.5 to 14 years (N = 111)</u> β = -7.16 (4.37) p = 0.11 <u>14 to 17 years (N = 114)</u> β = -3.52 (3.46) p = 0.31 <u>0 to 17 years (N = 104)</u> β = -0.06 (5.52) p = 0.99	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			• Change (SE) in compression strength (mg^2/mm^4) per 1 mg unit increase in daily fluoride intake during the specified time period among boys 0 to 8.5 years (N = 124) β = 10.96 (7.81) p = 0.17 8.5 to 14 years (N = 111) β = 7.53 (6.92) p = 0.28 14 to 17 years (N = 114) β = 10.58 (5.22) p = 0.05 0 to 17 years (N = 104)	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			β = 9.37 (8.34) p = 0.27 • Change (SE) in torsion strength (mm^3) per 1 mg unit increase in daily fluoride intake during the specified time period among boys 0 to 8.5 years (N = 124) β = 93.65 (87.79) p = 0.29 8.5 to 14 years (N = 111) β = 72.06 (74.95) p = 0.34 14 to 17 years (N = 114) β = 175.06 (56.42) p = <0.01	

Study characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			0 to 17 years (N = 104) β = 90.24 (95.28) p = 0.35	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were adolescents (17 years of age), whose families were recruited from Iowa hospitals following birth. The time of sampling for the Iowa Fluoride Study (IFS) was from 1992 to 1995, and for the Iowa Bone Development Study (IBDS), a subset of IFS, was from 1998 to 2000.

Risk of bias assessment			
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Mutlivariable regression models were adjusted for height, weight, time since PHV [Peak Height Velocity], calcium and protein intake, and physical activity
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion and missing data were reported. Specifically, [n]ine tibial scans at 4% and 38% combined had movement artifacts and were excluded from the analyses. [a] 20% lower sample size resulted when calcium, protein, and physical activity were added to the model due to missing data." Interpolation was used when assessing fluoride intake: period-specific daily fluoride intakes in mg F/day were determined... using area-under-the-curve (AUC). Each AUC required data at the upper and lower endpoints,

Risk of bias assessment			
			with endpoints allowed to be interpolated from estimates within 7 months of the stated endpoints. The cumulative 'average' daily fluoride intake in mg from birth to age 17 years was calculated using AUC, with the requirements that each participant have at least one daily fluoride intake estimate recorded, obtained or interpolated for each of the period-specific fluoride intakes. If a time point was missing, linear interpolation using the nearest two points to the required time point was done.
Detection	Can we be confident in the exposure characterization?	–	Fluoride intake was assessed using multiple questionnaires, and considered the following sources of exposure: ... water, other beverages, selected foods, dietary fluoride supplements, and ingested fluoride toothpaste. The study authors state that "[f]luoride intakes for the study participants were based on parent and adolescent reports of ingested fluoride-containing products, which is an indirect method of quantifying intake, limited to fluoride assay results, and

Risk of bias assessment			
			possesses several limitations in terms of its reliability and validity.
	Can we be confident in the outcome assessment?	++	Participants were followed from birth to 17 years of age. Trabecular and cortical bone characteristics of the radial and tibial bone were determined using peripheral quantitative computed tomography (pQCT). Radiographic imaging was performed by certified technicians.
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the methods section were reported on in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Quadri 2018[xxviii] [80]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original pilot study **Study design:** Case-control (Only cross-sectional analysis results relevant to the review are included) **Country:** India	**Exposure:** <u>Fluoride levels in</u> • Urine samples • Serum samples **Method of exposure assessment:** • Measured using potentiometric method with fluoride selective ion electrode **Exposure levels:** **Urinary fluoride, mean ±SD**	**Outcomes:** <u>Nephrotoxicity:</u> • Renal tubule ultrastructural changes • Renal tubule apoptosis **Method of outcome ascertainment:** <u>Renal biopsy</u> • Suggested for G-1 and G-2 participants who had kidneys of regular size with no blockage and proteinuria, but the cause was unknown	**Statistical analysis:** • One-way analysis of variance (ANOVA) or Student's t test used to statistically compare groups • Results were identified as statistically significant at $p < 0.05$ **Results:** <u>Ultrastructural changes</u> • TEM images showed accumulation of multiple dark spherical microparticles within the tubular basement membranes… and	• Increased levels of apoptosis were observed in high fluoride group (Gp 2) compared to normal fluoride group (Gp 1), which leads to cell death and renal injury. • Various degrees of fluoride-associated damages to the architecture of tubular epithelia, such as cell swelling and lysis, cytoplasmic vacuolation, nuclear condensation, apoptosis, and necrosis, were observed.

[xxviii] Quadri et al. 2018: Although study is designed primarily as case-control studies, only results from the cross-sectional analysis were relevant to this review. Therefore, study was assessed for quality as cross-sectional using the OHAT risk of bias tool.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Children (4 to 12 years of age) with nephrotic syndrome minimal change disease (NS-MCD) from All India Institute of Medical Sciences' department for pediatric outpatients **Sampling time frame:** June 2012 - January 2015 **Sample size (N):** 156 <u>Group 1 (G-1): Nephrotic syndrome</u>	• Gp 0: 0.56 ppm ±0.15 • Gp 1: 0.61 ppm ±0.17 • Gp 2: 4.01 ppm ±1.83 **Serum fluoride, mean ±SD** • Gp 0: 0.07 ppm ±11 • Gp 1: 0.07 ppm ±0.01 • Gp 2: 0.1 ppm ±0.013 • Significantly higher level of fluoride in urine was reported among participants in G-2 than those in G-1 and G-0 (p = 0.001) • Significantly higher level of fluoride in serum was reported among participants in G-2 than those in G-1 and G-0 (p = 0.001)	• Ultrasounds were used to guide the procedure • Biopsy gun was used to acquire kidney tissues • A nephrologist and/or interventional radiologist conducted the procedure <u>Ultrastructural changes of kidney tissues</u> • Transition electron microscopy (TEM) <u>Renal tubule apoptosis</u> • Terminal deoxynucleotidyl transferase deoxyuridine triphosphate (dUTP) nick end labeling (TUNEL) assay	basement membrane disintegration… in Gp 2 • Glycogen lysis, rarefactions of cytoplasmic ground substances, hypervacuolation, and chromosome condensation were observed frequently … in the renal tubule of Gp 2 while the same was less frequent in Gp1. • The increased levels of nuclear swelling, chromatin disintegration, and other signs of apoptosis were observed in G-2 as compared to Gp 1. • The pyknotic changes in the cells of the renal tubules of G-2 observed but it was only occasional.	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
patients (NSP) with normal fluoride levels in urine (≤ 1 ppm) • N = 32 Group 2 (G-2): NSP with high fluoride levels in urine (> 1 ppm) • N = 32 Group 0 (G-0): Healthy controls matched by age with normal fluoride levels in urine (≤ 1 ppm) • N = 32 **Sex:** NR **Exclusions:** NR			Renal tubule apoptosis • Level of renal tubule apoptosis among participants in G-1 and G2 G-1 = 7% G-2 = 22% p = 0.001	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding/ support: None **Author declaration of interest:** None				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were children (4 to 12 years of age) with nephrotic syndrome minimal change disease (NS-MCD) from All India Institute of Medical Sciences'

Risk of bias assessment			
			department of pediatric outpatients. The study period was from June 2012 to January 2015. Each study group has the same number of participants.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	ANOVA or t-tests were used to conduct statistical comparisons between study groups.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	N of childhood nephrotic syndrome patients recruited = 156; however, N in group 1 = 32, N in group 2 = 32, and N in healthy controls or group 0 = 32
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in urine and serum samples. No differences in exposure assessment methods were reported between study groups.
	Can we be confident in the outcome assessment?	+	Ultrastructural and apoptotic analysis was conducted with transmission electron microscopy and terminal deoxynucleotidyl transferase deoxyuridine

Risk of bias assessment			
			triphosphate nick end labelling, respectively. Blinding status unlikely to affect outcome assessment.
Selective reporting	Were all measured outcomes reported?	+	Ultrastructural changes in kidney tissues and apoptosis in kidney tubules were mentioned in the methods section. Ultrastructural changes were described in more specific details in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	+	Insufficient information on participants available (i.e. patient characteristics, general place of residence, etc.).

Rathore 2018 [81]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original Study **Study design:** Cross-sectional study **Country:** India **Participants:** Children (8 to 14 years of age) from Jodhpur district villages of Rajasthan **Sampling time frame:** NR	**Exposures:** Fluoride levels in • Drinking water samples • Urine samples • Blood samples **Method of exposure assessment:** Drinking water samples: • Electrochemical method Urine and blood samples • F ion specific electrode Exposure groups	**Outcomes:** Thyroid hormone derangement • Serum levels of free T4 (FT4), free T3 (FT3), and thyroid stimulating hormone (TSH) **Method of outcome ascertainment:** • Chemiluminescence Assay	**Statistical analysis:** NR **Results:** • Free T3: mean, ±SD, [range] (pg/mL) *Gp 1: 2.66 pg/mL ±0.46, [2.11 – 3.89]* *Gp 2: 2.73 pg/mL ±0.36, [2.13 – 3.56]* *Gp 3: 2.84 pg/mL ±0.46, [2.02 – 4.26]* *Gp 4: 3.06 pg/mL ±0.78, [1.91 – 4.42]* • Free T4: mean ±SD, [range] (ng/dL) *Gp 1: 0.98 ±0.21, [0.79 – 1.79]*	• When serum FT3, FT4 and TSH of different category of our study were compared we found significant difference between these. • FT3 levels was highest in gp 4 with minor difference in other groups; concentration of FT4 levels was maximum in gp 3, whereas TSH levels were significantly higher in gp 4. • As the level of fluoride increases in drinking water, levels of thyroid hormones were also increased but the levels were not as significantly higher as other studies.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sample size (N): 100 • N = 25 per exposure group **Sex:** NR **Exclusions:** "Children who were not the permanent residents of that particular area and with a change of source of drinking water, those with orthodontic brackets, dentofacial deformities or any syndromes or uncooperative,	• Villages were categorized based on fluoride levels in drinking water, yielding the following exposure groups: Gp 1: <1ppm Gp 2: 1-1.9 ppm Gp 3: 2-3.9 ppm Gp 4: ≥ 4ppm **Exposure levels:** • **Urinary fluoride, mean ±SD** ○ *Gp 1: 1.25 mg/L ±0.42* ○ *Gp 2: 1.23 mg/L ±0.32* ○ *Gp 3: 3.03 mg/L ±0.58* ○ *Gp 4: 4.49 mg/L ±1.21* • **Serum fluoride, mean ±SD**		*Gp 2: 1.02 ±0.26, [0.78 – 1.89]* *Gp 3: 1.11 ±0.28, [0.76 – 1.98]* *Gp 4: 1.22 ± 0.33, [0.75 – 1.89]* • TSH: Mean ± SD, [range] (µIU/mL) *Gp 1: 1.33 ±0.78, [0.4 – 2.99]* *Gp 2: 1.64 ±0.88), [0.29 – 3.76]* *Gp 3: 1.86 ±0.77, [0.76 – 3.74]* *Gp 4: 1.91 ±1.10, [0.75 – 4.99]*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
medically and physically compromised patients…" (p. 328) **Source of funding/ support:** NR **Author declaration of interest:** NR	○ *Gp 1: 0.046 mg/L ±0.02* ○ *Gp 2: 0.046 mg/L ±0.02* ○ *Gp 3: 0.11 mg/L ±0.09* ○ *Gp 4: 0.20 mg/L ±0.13*			

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants were children from Jodhpur district villages of Rajasthan. Recruitment time frame and participation rate between exposure groups not found.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Children who were not the permanent residents of that particular area and with a change of source of drinking water, those with orthodontic brackets, dentofacial deformities or any syndromes or uncooperative, medically and physically compromised patients were excluded from the study. Sample sizes were the same across exposure groups (N = 25).

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in drinking water, urine, and blood. No difference in exposure assessment methods were found between exposure groups.
	Can we be confident in the outcome assessment?	++	FT3, FT4, and TSH were measured in serum, and therefore are unlikely to be affected by blinding status.
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the abstract were reported on in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	+	No description of the statistical methods used in the analysis.

Shruthi 2018 [82]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** India **Participants:** Individuals living in randomly selected villages of Bangarpet taluk, Kolar. Study groups are comprised of areas with high (Thimmasandra and	**Exposure:** <u>Fluoride levels in</u> • Drinking water samples **Method of exposure assessment:** • Measured using ion-electrode method • Used to calculate exposure dose which takes into consideration Fluoride level (mg/L) Water intake/day (L/day) Body weight (kg) **Exposure levels:**	**Outcomes:** Non-skeletal manifestations of fluoride toxicity **Method of outcome ascertainment:** <u>Evaluated using clinical history for the following:</u> • Dyspepsia with nausea, vomiting, abdomen pain, constipation, or diarrhea • Muscle weakness • Tiredness • Fatigue • Polyuria • Polydipsia	**Statistical analysis:** Frequency between study groups **Result:** • Number (%) of participants with non-skeletal manifestations of fluorosis by study groups <u>Dyspepsia = 32 (100.0)</u> High fluoride group = 24 (75.0) Normal fluoride group = 8 (25.0)	• Higher proportion of study subjects with clinical manifestations of non-skeletal fluorosis compared to those without clinical manifestations of non-skeletal fluorosis at nearly same doses of fluoride exposure in both high and normal fluoride groups indicates that these manifestations may be due to fluoride exposure through water or other sources like food. • Participants with dyspepsia in the high fluoride group are three-times higher than those in the normal fluoride group.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Batwarahalli) and normal (Maddinayakanahalli) levels of fluoride in water. The median (interquartile range) age of participants is 30 (18.75 – 45) years in the high fluoride group, and 33 (20 – 45) years in the normal fluoride group. **Sampling time frame:** Study duration of 1 year **Sample size (N):**	<u>High fluoride group</u> > 1.5 mg/L fluoride in water <u>Normal fluoride group</u> < 1.0 mg/L fluoride in water	• Recurrent abortions or stillbirths	<u>Muscle weakness = 13 (100.0)</u> High fluoride group = 9 (69.23) Normal fluoride group = 4 (30.77) <u>Fatigue = 32 (100.0)</u> High fluoride group = 19 (59.38) Normal fluoride group = 13 (40.62)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
<u>High fluoride group</u> • N = 486 <u>Normal fluoride group</u> • N = 417 **Sex:** <u>High fluoride group</u> • Men N (%): 245 (55.1) <u>Normal fluoride group</u> • Men (%) = 200 (44.9) **Exclusions:** • Has no teeth, • Has artificial teeth • Is pregnant • Is bedridden • Is not available following the second visit			• "None of the study participants had complaints of polyuria, polydipsia, repeated abortions, and repeated stillbirths…" (p. 1225) • "The study subjects with clinical manifestations of non-skeletal fluorosis were higher compared to those without clinical manifestations of non-skeletal fluorosis at nearly same doses of fluoride exposure in both high and normal fluoride groups…" (p. 1225)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding/ support: None **Author declaration of interest:** None				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable

Risk of bias assessment			
	Did selection of study participants result in appropriate comparison groups?	++	Participants consisted of individuals living in villages that were randomly selected from Bangarpet taluk, Kolar. Study groups were comprised of areas with high and normal levels of fluoride in water. The median (interquartile range) age of participants is 30 (18.75 – 45) years in the high fluoride group, and 33 (20 – 45) years in the normal fluoride group. The study duration was 1 year.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Persons with no teeth, artificial teeth, pregnant women, bedridden, and the persons who were not available even after two visits were excluded from the study. No mention of missing data.

Risk of bias assessment			
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in drinking water. No difference in exposure assessment methods were reported between participants.
	Can we be confident in the outcome assessment?	–	Clinical history of select conditions were used to determine non-skeletal fluorosis manifestations. Uncertain if outcome assessors were blinded to exposure status.
Selective reporting	Were all measured outcomes reported?	++	Outcomes mentioned in the methods section were also reported on in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Yu 2018 [83]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** China **Participants:** Random sample of children (7 to 13 years of age) from rural areas of Tianjin city with high and normal levels of fluoride	**Exposures:** Fluoride levels in • Urine samples • Drinking water samples **Method of exposure assessment:** Water samples • Public water supplies were randomly sampled per village (N = 168) • Measured using the national standardized ion selective electrode method Urine samples: • Early morning spot urine samples were acquired from	**Outcomes:** • Intelligence quotient (IQ) **Method of outcome ascertainment:** Second edition of the Combined Raven's Test – The Rural in China (CRT-RC2) • Used to determine IQ scores which was grouped as: Retarded: ≤ 69 Marginal: 70 – 79 Dull normal: 80 – 89 Normal: 90 – 109	**Statistical analysis:** • Piecewise linear regression and multiple logistic regression models were used to assess associations of interest • Stepwise linear regression models used to identify possible confounders • Models were adjusted for age, sex, paternal education, maternal education, and low birth weight **Results:** • Threshold effect analysis: Change (95% CI) in IQ scores per 0.5 mg/L increment of fluoride	• "In our study, urinary fluoride levels presented a positive relationship with water fluoride concentration, indicating that fluoride from drinking water makes important contribution to urinary fluoride." (p. 120) • "…chronic exposure to excessive fluoride, even at a moderate level, was inversely associated with children's … intelligence scores, especially excellent intelligence performance, with threshold and saturation effects observed in the dose-response relationships." (p. 123)

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: 2015 **Sample size (N):** 2,886 <u>Normal-fluoride exposure (water fluoride ≤ 1.0 mg/L)</u> • N = 1,636 <u>High-fluoride exposure (water fluoride > 1.0 mg/L)</u> • N = 1,250 **Sex:**	participants (N = 2,380) • Measured using the national standardized ion selective electrode method **Exposure levels:** • Mean (SD) levels of fluoride in water (mg/L) (p <0.001) <u>Normal-fluoride exposure</u> 0.50 (0.27) <u>High-fluoride exposure</u> 2.00 (0.75) • Mean (SD) levels of fluoride in urine (mg/L) (p <0.001) <u>Normal-fluoride exposure</u>	High normal: 110 – 119 Superior: 120 – 129 Excellent: ≥ 130 • The validated test was independently completed by participants within 40 minutes and this was overseen by four trained professionals	in water by concentration ranges <u>0.20 – 3.40 mg/L</u> β = -0.04 (- 0.33, 0.24) <u>3.40 – 3.90 mg/L</u> β = - 4.29 (- 8.09, - 0.48) • Threshold effect analysis: Change (95% CI) in IQ scores per 0.5 mg/L increment of fluoride in urine by concentration ranges <u>0.01 – 1.60 mg/L</u> β = 0.36 (- 0.29, 1.01) <u>1.60 – 2.50 mg/L</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
<u>Normal-fluoride exposure</u> • Boys N (%): 849 (51.9) <u>High-fluoride exposure</u> • Boys N (%): 667 (53.4) **Exclusions:** • Were not lifetime residents of the study area • Has a disease that impacts intelligence (congenital or acquired) • Has history of cerebral trauma or neurological disorders • Has history of a positive screening test for Down's syndrome or hepatitis	0.41 (0.49) <u>High-fluoride exposure</u> 1.37 (1.08)		β = -2.67 (-4.67, -0.68) <u>2.50 – 5.54 mg/L</u> β = -0.84 (-2.18, 0.50) • Odds (95% CI) of IQ level among children exposed to high water fluoride (> 1.0 mg/L) compared to normal water fluoride (≤ 1.0 mg/L); normal IQ is the control <u>Excellent IQ</u> OR = 0.47 (0.32, 0.71) <u>Superior IQ</u> OR = 0.89 (0.69, 1.15) <u>High normal IQ</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
B/treponema palladium infection • Gestational exposure to maternal smoking • Gestational exposure to maternal drinking **Source of funding/ support:** • State Key Program of National Natural Science of China, and the Fundamental Research Funds for the Central Universities **Author declaration of interest:** None			OR = 0.96 (0.80, 1.15) <u>Dull normal IQ</u> OR = 0.85 (0.62, 1.17) <u>Marginal IQ</u> OR = 1.25 (0.69, 2.26) • Odds (95% CI) of IQ level among children exposed to high urine fluoride (> 1.60 mg/L) compared to normal urine fluoride (≤ 1.60 mg/L); normal IQ is the control <u>Excellent IQ</u> OR = 0.49 (0.26, 0.93) <u>Superior IQ</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			OR = 0.84 (0.58, 1.20) <u>High normal IQ</u> OR = 0.87 (0.68, 1.12) <u>Dull normal IQ</u> OR = 0.63 (0.39, 1.01) <u>Marginal IQ</u> OR = 1.44 (0.72, 2.91) • Stratified threshold effect analysis: Odds (95% CI) of IQ level per 0.5 mg/L increment of fluoride in water; normal IQ is the control	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			Excellent IQ (Fluoride level of 0.20 – 1.40 mg/L) OR = 0.60 (0.47, 0.77) Excellent IQ (Fluoride level of 1.40 – 3.90 mg/L) OR = 1.09 (0.88, 1.36) Superior IQ OR = 0.99 (0.93, 1.06) High normal IQ OR = 0.98 (0.94, 1.03) Dull normal IQ OR = 0.96 (0.88, 1.05)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			<u>Marginal IQ</u> OR = 1.04 (0.89, 1.23) • Stratified threshold effect analysis: Odds (95% CI) of IQ level per 0.5 mg/L increment of fluoride in urine; normal IQ is the control <u>Excellent IQ</u> OR = 0.87 (0.76, 1.01) <u>Superior IQ</u> OR = 0.96 (0.89, 1.04) <u>High normal IQ</u> OR = 0.99 (0.94, 1.04) <u>Dull normal IQ</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			OR = 0.90 (0.81, 1.00) <u>Marginal IQ</u> OR = 1.07 (0.91, 1.25)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were a random sample of children (7 to 13 years of age) from rural areas of Tianjian City with high and normal levels of fluoride. The study was conducted in 2015 and the multistage random

Risk of bias assessment			
			sampling technique, stratified by area, was performed to select representative samples among local children who were permanent residents since birth.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Regression models were adjusted for age, sex, paternal education, maternal education, and low birth weight.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Of the 2886 children recruited, urine samples were acquired from 2380 participants. A total of 2886 children completed the IQ assessments.
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in drinking water and urine samples. No differences in exposure assessment methods were found between participants.
	Can we be confident in the outcome assessment?	++	IQ scores were determined using the Combined Raven's Test - The Rural in China (2nd Edition) which

Risk of bias assessment			
			is a validated test that was independently completed by participants within 40 minutes, and this was overseen by trained professionals. Outcome unlikely to be affected by blinding status.
Selective reporting	Were all measured outcomes reported?	++	Yes, the outcome mentioned in the abstract was reported on in the results section.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Arulkumar 2017[xxix] [84]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Case-control (Only cross-sectional analysis results are relevant to current review) **Country:** India	**Exposures:** <u>Fluoride levels in</u> • Serum **Method of exposure assessment:** • Venipuncture used to collect samples of overnight fasting blood • Measured using Orion Ion Analyser **Exposure level:** • Drinking water fluoride concentration: > 1.5 mg/l	**Outcomes:** <u>Degree of lipid peroxidation</u> • Plasma thiobarbituric acid reactive substance (TBARS) • Erythrocyte TBARS <u>Lipid profiles</u> • Cholesterol • Triglyceride (TGL) • High-density lipoprotein (HDL) • LDL • VLDL <u>Enzyme activity</u> • Paraoxonase (PON1) • Arylesterase (ARE) • Lactonase	**Statistical analysis:** • Pearson's correlation was used • Correlations at level of 0.05 and 0.01 (2-tailed) were identified as significant **Results:** Correlation between serum fluoride and outcomes in patients with fluorosis • <u>Plasma TBARS</u> r = 0.095; p = 0.019 • <u>Erythrocyte TBARS</u> r = 0.783; p = 0.000	• The PON1 and related activities such as ARE and lactonase were found to be reduced in fluorosis patients. It is ascribed from the findings that the toxic effect of fluoride collectively abrogates not only antiatherogenic activity but also reduces lactonase activity of PON1 thereby toxic HCy may get accumulated, which support the chances of cardiovascular related complications in fluorosis patients. • Positive correlation with erythrocyte

[xxix] Arulkumar 2017: Although study is designed primarily as case-control study, only results from the cross-sectional analysis were relevant to this review. Therefore, study was assessed for quality as cross-sectional using the OHAT risk of bias tool.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Fluorosis (dental and skeletal) cases and controls from 3 Tamil Nadu districts with high levels of fluoride in water (Salem, Dharmapuri, and Krishnagiri) **Sampling time frame:** NR **Sample size (N):** 508 <u>Group I (controls)</u> • N = 52 <u>Group II (mild fluorosis)</u>	• Mean (SD) level of fluoride (mg/L) in serum by study groups <u>*Group I (controls):*</u> *0.07 (0.08)* <u>*Group II (mild fluorosis):*</u> *0.13 (0.02)* <u>*Group III (moderate fluorosis):*</u> *0.19 (0.03)* <u>*Group IV (severe fluorosis):*</u> *0.28 (0.03)*	**Method of outcome ascertainment:** • Venipuncture used to collect samples of overnight fasting blood • Biochemical assays conducted at ≤ 2 days from sample collection <u>Erythrocyte and plasma TBARS</u> • Creatinine kinase (CK-MB) assay • Used to evaluate fluoride toxicity by identifying lipid peroxidation products <u>TGL and HDL</u> • AGAPPE diagnostic kit	• <u>Cholesterol</u> r = 0.121; p = 0.003 • <u>TGL</u> r = -0.043; p = NS • <u>HDL</u> r = -0.075; p = 0.006 • <u>LDL</u> r = 0.157; p = 0.000 • <u>VLDL</u> r = -0.038; p = NS • <u>PON1</u> r = -0.738; p = 0.000 • <u>ARE</u> r = -0.447; p = 0.000 • <u>Lactonase</u> r = -0.645; p = 0.000 Activity of membrane bound and pesticide scavenging enzymes in fluorosis patients.	TBARS (p < 0.01), plasma TBARS (p < 0.05), cholesterol (p < 0.01) and LDL (p < 0.01). • Significant inverse association of serum fluoride levels with PON1, ARE, and lactonase. • No significant association of serum fluoride levels with TGL and VLDL. • No observed correlation with serum HDL; however, serum fluoride modulates the activities of PON1, ARE and lactonase. • Increased LDH5 isoenzyme (liver synthesized) activity is an indication of possible liver damage in fluorosis patients. Therefore, it was concluded that the

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• N = 112 Group III (moderate fluorosis) • N = 136 Group IV (severe fluorosis) • N = 208 **Sex (N):** Group I (controls) • Men = 28; Women = 24 Group II (mild fluorosis) • Men = 76; Women = 36 Group III (moderate fluorosis) • Men = 78; Women = 58		Other parameters of blood • Standard protocols PON1 • p-nitrophenol released at 412 nm used to determine enzyme activity ARE • Enzyme activity determined using absorbance of phenylacetate at 270 nm Lactonase activity • UV-visible spectrophotometer used to determine absorbance at 270 nm	Serum level of AChE (U/l) • Controls: 6.29 ± 0.68 • Mild: 4.64 ± 0.54 • Moderate: 4.11 ± 0.4 • Severe: 3.78 ± 0.35 Serum level of ATPase/Na+ K+ ATPase • Controls: 2.41 ± 0.34 • Mild: 2.56 ± 0.31 • Moderate: 2.64 ± 0.29 • Severe: 2.87 ± 0.4	prolonged fluoride ingestion (observed in moderate and severe groups) caused continuous multifaceted calamities beyond the regenerative capacity of the liver tissues.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Group IV (severe fluorosis) • Men = 112; Women = 96 **Exclusions:** • "…smoking, heart, liver/kidney disease, cancer, chronic inflammation, autoimmune and hematological disorders." (p. 207) **Source of funding/ support:** Periyar University, and Indian Council of Medical Research		Serum level of AChE and ATPase/Na+ K+ ATPase • AChE: described by Ellman et al. [17] • ATPase: measured by estimating the liberated inorganic phosphorus (Pi), after the reaction of erythrocytes homogenate with ATP [18]. • Total ATPase: assayed using UV−vis spectrophotometer at 660 nm.		

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: NR				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants were from 3 Tamil Nadu (India) districts with high levels of fluoride in water. Recruitment time frame not found.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR

Risk of bias assessment			
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided for the study. "Exclusion criteria were smoking, heart, liver/kidney disease, cancer, chronic inflammation, autoimmune and hematological disorders." (p. 207) There was no mention of missing data.
Detection	Can we be confident in the exposure characterization?	++	Fluoride was measured in serum. No difference in exposure assessment methods were found between participants.
	Can we be confident in the outcome assessment?	++	Outcome levels were measured using blood samples, and therefore are unlikely to be affected by blinding status.
Selective reporting	Were all measured outcomes reported?	++	Outcomes mentioned in the methods section were also reported on in the results section.

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Bashash 2017 [85]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Prospective cohort study	**Exposures:** <u>Fluoride levels in</u> • Maternal urinary samples during gestation (proxy measure of prenatal exposure to fluoride) • Child urinary samples at 6 to 12 years of age (proxy measure of postnatal exposure to fluoride)	**Outcomes:** Neurocognitive function in children at 4 years of age, and 6 to 12 years of age **Method of outcome ascertainment:**	**Statistical analysis:** • Linear regression models were used • Models assessing maternal urinary fluoride levels as exposure were adjusted for child characteristics (gestational age, birth weight, sex, parity, age at outcome assessment) and	• Higher prenatal exposure to fluoride (as indicated by average creatinine-adjusted maternal urinary fluoride concentrations during pregnancy) was associated with lower GCI scores in children at approximately 4y old, and with lower Full-

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Country: Mexico **Participants:** Mother-child pairs from three hospitals in Mexico City that were enrolled in two of four cohorts of the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study; specifically, participants from cohorts 2A and 3 were included in the analysis **Sampling time frame:**	**Method of exposure assessment:** • Second morning void spot urine sample • Ion-selective electrode-based assays used to measure fluoride in most samples • Maternal fluoride levels in urinary samples were adjusted for creatinine • Child fluoride levels in urinary samples were adjusted for specific gravity **Exposure levels:** **Water fluoride levels in Mexico City:**	<u>Standardized version of McCarthy Scales of Children's Abilities (MSCA)</u> • Completed at 4 years of age • Used to acquire a standardized composite score called the General Cognitive Index (GCI) <u>Wechsler Abbreviated Scale of Intelligence (WASI)</u> • Completed at 6 to 12 years of age • Used to acquire Full-Scale IQ <u>Other Details</u> • Experienced developmental psychologist trained and oversaw the	maternal characteristics (smoking history, marital status, delivery age, IQ, education, and cohort) • Models assessing child urinary fluoride levels were adjusted for the main covariates of interest **Results:** Change (95% CI) in outcome per 0.5 mg/L increase in maternal urinary fluoride levels adjusted for creatinine • <u>GCI</u> β = -3.15 (-5.42, -0.87)	Scale IQ scores at 6–12 y old. • In models that focused on the cross-sectional relationship between children's exposure to fluoride (reflected by their specific gravity–adjusted urinary fluoride levels) and IQ score and that contained the main covariates of interest, there was not a clear, statistically significant association between contemporaneous children's urinary fluoride (CUFsg) and IQ either unadjusted or adjusting for MUFcr

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
<u>Cohort 2A:</u> • May 1997 – July 1999 <u>Cohort 3</u> • 2001 to 2003 **Sample size (N):** 299 mother-child pairs **Sex:** <u>GCI analysis: Girls</u> • N (%) = 160 (56) <u>IQ analysis: Girls</u> • N (%) = 116 (55) **Exclusions:**	○ *0.15 - 1:38 mg/L (Juárez-Lópezetal.2007; Martínez-Mier et al.2005).* **Maternal urinary fluoride (Mean ±SD)** ○ *0.88 mg/L ±0.34* **Child urinary fluoride (Mean ±SD)** *0.84 mg/L ±0.40*	administration of tests by three other psychologists • Psychologist conducting the assessment was blinded to the child's exposure level	p = 0.01 • <u>IQ</u> β = -2.50 (-4.12, -0.59) p = 0.01 Change (95% CI) in outcome per 0.5 mg/L increase in child urinary fluoride levels adjusted for specific gravity • <u>IQ – Without adjustment of maternal urinary fluoride levels</u> β = - 0.89 (-2.63, 0.85) • <u>IQ – With adjustment of maternal urinary fluoride levels</u>	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• No gestational urine sample available (Cohort 1 and 2B) • > 14 gestational weeks at recruitment • Do not intend to reside in study area for ≥ 5 years • History of psychiatric disorders, pregnancies that are high-risk, or gestational diabetes • Daily alcohol consumption • Illegal/prescription drug use • Have kidney disease, high blood pressure, preeclampsia, circulatory disease, and seizures during gestation • No neurocognitive function measurement in the child			β = - 0.77 (-2.53, 0.99)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Source of funding/ support: NIH, NIEHS/EPA, and the National Institute of Public Health/Ministry of Health of Mexico; facilities provided by the American British Cowdray Hospital **Author declaration of interest:** No competing financial interests				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were mother-child pairs from three hospitals in Mexico City that were enrolled in two of four cohorts of the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study. Time of recruitment was from May 1997 to July 1999 for cohort 2A and 2001 to 2003 for cohort 3; however, mean maternal urinary fluoride levels adjusted for creatinine was not significantly different between groups (Cohort 3 - Intervention; Cohort 3 - Placebo; Cohort 2A).
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Regression models were adjusted for child characteristics (gestational age, birth weight, sex, parity, and age at outcome assessment), and maternal characteristics (smoking history, marital status, age at delivery, IQ, education, and cohort).

Risk of bias assessment			
			We also note that the coefficients for the associations between fluoride on cognition varied substantially in some of the sensitivity analyses, particularly with respect to the subgroups of participants who have data on SES, lead exposure, and mercury exposure (of which, for the latter, the effect estimates almost doubled).
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	Reasons for exclusion were documented. N = 512 for pregnant women with data on fluoride and creatinine; N = 312 and 234 for children with data on GCI and IQ, respectively; N = 287 for children with GCI and complete covariate data; N = 211 for children with IQ and complete covariate data. In the comparisons of participants in relation to missing data ..., the proportion of females was

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Risk of bias assessment					
			somewhat higher in the included versus excluded group for both the GCI and IQ analyses, and the mean levels of maternal blood Hg for those included were 28.5% and 24.9% higher than the mean levels for those excluded in the GCI and IQ analyses, respectively. We also note that the coefficients for the associations between fluoride on cognition varied substantially in some of the sensitivity analyses, particularly with respect to the subgroups of participants who have data on SES, lead exposure, and mercury exposure (of which, for the latter, the effect estimates almost doubled).		
Detection	Can we be confident in the exposure characterization?	+	Fluoride levels were measured in maternal and child urinary samples. A relatively smaller number of prenatal samples were assessed at a different lab because the quality control criteria for ion-selective electrode-based methods were not met.		
	Can we be confident in the outcome assessment?	++	Participants were recruited at 14	++	Participants were recruited at 14

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Risk of bias assessment					
			gestational weeks or less. General Cognitive Index (GCI) was acquired using the standardized version of the McCarthy Scales of children's Abilities (MSCA) at age 4. An experienced developmental psychologist trained and oversaw the administration of the tests by three other psychologists. As well, the psychologist conducting the assessment was blinded to the child's exposure level.		gestational weeks or less. Full-Scale IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI) at age 6 to 12. An experienced developmental psychologist trained and oversaw the administration of the tests by three other psychologists. As well, the psychologist conducting the assessment was blinded to the child's exposure level. Regression models were adjusted for the age at outcome assessment.

Risk of bias assessment				
			Regression models were adjusted for the age at outcome assessment.	
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the abstract were also reported on in the results section.	
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.	

Chauhan 2017 [4]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Abstract **Study design:** NR **Country:** India **Participants:** Population exposed to fluoride **Sample size (N):** 100 **Sex:** Men (100%)	**Exposure:** • Fluoride **Method of exposure assessment:** NR **Exposure level:** NR	**Outcomes:** • Semen morphological parameters • Hypothalamic-testicular axis hormones (LH, FSH, prolactin, testosterone) • Oxidative stress markers **Method of outcome ascertainment:** NR	**Statistical analysis:** NR **Results:** • "LH, FSH, testosterone and prolactin values was significantly ($p<0.05$) alters in fluoride exposed population." (p. S236) • "Increased lipid peroxidation and Protein carbonyl content and decreased antioxidant status i.e., SOD, CAT, GPx and GSH was observed." (p. S236) • "Sperm count, motility and viability was delineated in exposed population." (p. S236)	• "This study suggests that hypothalamic testicular axis hormones and oxidative stress parameters can be useful as early markers for determination of disease fluorosis in population those residing in high fluoride regions." (p. S236)

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Exclusions: NR **Source of funding/ support:** NR **Author declaration of interest:** NR				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable

Risk of bias assessment			
	Did selection of study participants result in appropriate comparison groups?	NA	Abstract
Confounding	Did the study design or analysis account for important confounding and modifying variables?	NA	Abstract
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	NA	Abstract
Detection	Can we be confident in the exposure characterization?	NA	Abstract
	Can we be confident in the outcome assessment?	NA	Abstract
Selective reporting	Were all measured outcomes reported?	NA	Abstract

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	NA	Abstract

Stephenson 2017 [5]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference Type: Abstract **Study design:** NR **Country:** US **Participants:** NR	**Exposure:** • Fluoridated water **Method of exposure assessment:** • State data from the CDC **Exposure levels:** NR	**Outcomes:** • Suicide rates **Method of outcome ascertainment:** • NR	**Statistical analysis:** • Correlation coefficients **Results** • Relationship between fluoridated water and suicide rates: <u>Year 2010</u> r= -0.386; p= 0.05 <u>Year 2012</u>	• These results suggest that… fluoridation may be correlated with a decrease in the rate of suicide by reducing the levels of microorganisms found in drinking water.

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: 2010, 2012, and 2014 **Sample size (N):** NR **Sex:** NR **Age:** NR **Exclusions:** NR **Source of funding/ support:** USTAR			r= -0.324; p= 0.020 <u>Year 2014</u> r= -0.342; p= 0.014	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: NR				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	NA	Abstract
Confounding	Did the study design or analysis account for important confounding and modifying variables?	NA	Abstract
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	NA	Abstract
Detection	Can we be confident in the exposure characterization?	NA	Abstract
	Can we be confident in the outcome assessment?	NA	Abstract
Selective reporting	Were all measured outcomes reported?	NA	Abstract
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	NA	Abstract

Verma 2017 [86]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** India **Participants:** High school adolescents (12–17 years) from randomly selected government and private schools in urban and rural areas of Kolar	**Exposures:** Fluoride levels in ground water **Method of exposure assessment:** The Orion method (Selective Electrode fluoride estimation apparatus) **Exposure level:** Mean water fluoride: • Holur: 0.85 mg/L. • Other 5 villages: ≥1.2 mg/L • All 6 villages: 1.4 ±0.38	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** • Dental examination using Dean's fluorosis index • Community fluorosis index (CFI)	**Statistical analysis:** • Chi-square test • Multivariable analysis with generalized estimating equation (GEE) regression model **Results:** Karl Pearson correlation coefficient (all 6 villages) • Mean fluoride level in water: 1.4 mg/L ± 0.38 • Community fluorosis index: 2.3 ± 0.37 Multivariable regression analysis (GEE) by drinking water source: • Fluorosis present:	"Prevalence of dental fluorosis was considerably high, affecting nearly two-thirds of the students, and mainly in government schools and long-term residents of the area."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
taluka (6 villages). All students who were residents of the area since birth were included in the study. **Sampling time frame:** February - August 2013 **Sample size:** 1,026 **Sex (N):** Boys: 509 (49.6%) **Exclusions:**			○ Bore well water: 551 (63.7%) ○ Pipe/tape water: 79 (64.8%) • Total: ○ Bore well water: 865 ○ Pipe/tape water:122 • β estimate (95%CI): ○ Bore well water: 0.92(−0.32,2.16), p-value: 0.145 ○ Pipe/tape water: 0	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
NR **Source of funding / support:** None **Author declaration of interest:** • No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable

Risk of bias assessment			
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Yes, it accounted for some confounders such as fluoridated toothpaste, consumption of finger millet and tea.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	-	Insufficient information provided on reasons for exclusion of participants
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using the Orion method (Selective Electrode fluoride estimation apparatus).
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by a dental specialist using Dean's Fluorosis Index and Community fluorosis index (CFI). Lack of blinding of

Risk of bias assessment			
			outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Cardenas-Gonzalez 2016 [87]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
	Exposures:	**Outcomes:**	**Statistical analysis:**	• The correlation of … fluoride levels

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:** Mexico **Participants:** Children (5 to 12 years of age) residents of Villa de Reyes County of San Luis Potosi, who were between grades 1 to 6 at two public elementary schools	<u>Fluoride levels in</u> • Urine samples • Drinking water samples **Method of exposure assessment:** <u>Urine Samples</u> • One spot urine sample used • Ion selective electrode was used to measure fluoride <u>Water samples</u> • Water samples were collected on March 2015 • tap and bottled water samples were acquired from 63 participants • Well water samples were acquired at	<u>Kidney injury biomarkers</u> • Kidney injury molecule 1 (KIM-1) • Neutrophil gelatinase-associated lipocalin (NGAL) • Serum creatinine (SCr) • MircroRNAs (miRNAs): miR-21, miR200c, and miR-423 • Estimated glomerular filtration rate (eGFR) • Albumin-creatinine ratio (ACR) **Method of outcome ascertainment:** <u>KIM-1 and NGAL</u> • Micro-bead assays • Measured in urine samples	• Spearman's correlation and linear regression models were used. • Model 1 was adjusted for age, sex, and BMI z-score • Model 2 was adjusted for model 1 covariates and urinary specific gravity • Model 3 was adjusted for model 1 covariates and urinary creatinine **Results:** Correlation between urinary levels of fluoride (ppm) and kidney injury biomarkers: • <u>KIM-1 (pg/mL)</u>	between urine and water samples was significant… suggesting that water is the main source of fluoride exposure. • Urinary miR-200c was correlated with… fluoride... There was no correlation between any of the other biomarkers and toxicants exposure levels. • Regression models examining the association between urine… fluoride… and the kidney injury biomarkers did not show any statistically significant differences (data not shown).

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sampling time frame: June 2014 **Sample size (N):** 83 **Sex:** <u>Boys</u> N (%) = 47 (56.63) **Exclusions:** • Were not lifetime residents of the study area • Girls with menarche • Has congenital kidney disease or urinary tract infections	various depths (1 m = superficial; 100 m = middle; 130 m = deep) from three water systems that are local • Ion selective electrode was used to measure fluoride **Exposure level:** **Tap water fluoride, mean (range)** ○ *2.47 ppm (2.08 - 2.94)* **Urinary fluoride, mean (range)** *2.18 ppm (0.34 - 8.60)*	<u>Urinary albumin, urinary creatinine, and SCr</u> • Daytona auto-analyzer <u>miRNAs</u> • RNA isolation, reverse transcription, pre-amplification, qPCR, and quantification • Measured in urine samples	r = 0.09; p = 0.38 • <u>NGAL (ng/mL)</u> r = -0.2; p = 0.07 • <u>miR-21 (copies/µl)</u> r = 0.05; p = 0.67 • <u>miR-200c (copies/µl)</u> r = 0.27; p = 0.01 • <u>miR-423 (copies/µl)</u> r = 0.14; p 0.22 • <u>SCr (mg/dL)</u> r = 0.07; p = 0.53 • <u>eGFR (mL/min)</u> r = - 0.19; p = 0.07 • <u>ACR (mg/gCr)</u> r = 0.08; p = 0.45 Regression analysis • No statistically significant differences reported between fluoride levels in urine	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
• Nonsteroidal anti-inflammatory drugs or antibiotics use			and outcome biomarkers	
Source of funding/ support: • National Council on Science and Technology • Fundacion Mexico en Harvard • A. C., NIH/NIEHS • Harvard-NIEHS Centre for Environmental Health • HSPH-NIEHS				
Author declaration of interest: None				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Participants were children (5 to 12 years of age) from Villa de Reyes county of San Luis Potosi, who were between grades 1 to 6 at two public elementary schools. The time of sampling for the study was June 2014.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	Model 1 was adjusted for age, sex, and BMI z-score. Model 2 was adjusted for model 1 covariates and urinary specific gravity. Model 3 was adjusted for model 1 covariates and urinary creatinine.
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable

Risk of bias assessment			
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Reasons for exclusion were provided for the study. "Of the initial 107 child participants, we excluded 16 with no urine or blood sample and 8 with an incomplete questionnaire." (p. 655)
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in urine and tap water samples. No difference in exposure assessment methods were found between participants.
	Can we be confident in the outcome assessment?	++	Several kidney injury biomarkers were measured in urine (KIM-1, NGAL, miR-21, miR-200c, miR-423, creatinine) or serum (creatinine). Other biomarkers of kidney injury assessed include the estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR), where albumin was measured in urine.
Selective reporting	Were all measured outcomes reported?	+	All outcomes mentioned in the methods section were reported on in the results section. Although spearman correlation coefficients and p-values were reported for the association between fluoride and outcomes, regression estimates were not provided but indicated as not being statistically different.

Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

de Moura 2016 [88]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional **Country:**	**Exposures:** Fluoride levels in • Water **Method of exposure assessment:** NR	**Outcome(s):** Dental fluorosis **Method of outcome ascertainment:** Assessment conducted by dental surgeons	**Statistical analysis:** • Prevalence of dental fluorosis • Descriptive data analysis **Results:** • The prevalence of fluorosis was 77.9% (n = 445).	"The prevalence of fluorosis was high, though the severity was low in individuals exposed to fluoridation since birth."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Brazil **Participants:** 11 to 14-year-old school children with fully erupted permanent teeth, signed informed consent, and completed socio-demographic questionnaire. **Sampling time frame:** 2011 **Sample size:** 571 (out of 596)	**Exposure level:** 0.6-0.8 ppm (as reported by the same author in in earlier study (Moura et al. 2010), for the same city of residence of the study participants	using the Thylstrup-Fejerskov (TF) Index	• 12.1% (n = 69) of all participants had fluorosis of TF3, and 0.4% of TF4 and TF5 (n=2). • Of the participants with higher severity of fluorosis: ○ *98.6% (n = 70) belonged to the lowest social class (≥ B2),* ○ *91.5% were born and always lived in Teresina,* ○ *94.4% consumed fluoridated water supply* ○ *76% used infant toothpaste, and* *64% reported swallowing this toothpaste*	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex (N): NR **Exclusions:** • Children with imperfect amelogenesis • Children undergoing fixed orthodontic treatment at the time of the assessment. • Children who were absent on the day of clinical examination **Source of funding / support:** NR				

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: NR				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable

Risk of bias assessment			
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (children with imperfect amelogenesis, undergoing fixed orthodontic treatment at the time of the assessment, or those who were absent on the day of clinical examination).
Detection	Can we be confident in the exposure characterization?	-	NR
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by dental surgeons using the Thylstrup-Fejerskov (TF) Index. Dentists were blinded to participants' clinical condition and residence.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were	++	None identified

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Risk of bias assessment			
	appropriate and researchers adhered to the study protocol)?		

Heck 2016 [89]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Dissertation **Study design:** Cross-sectional study **Country:** U.S.	**Exposures:** • Fluoridated water **Method of exposure assessment:** • Data from the 1992 Fluoridation Census and the 1990 Census were combined to acquire the proportion of individuals with optimally fluoridated water in a county	**Outcomes:** • Trouble working • Retardation • General health **Method of outcome ascertainment:** <u>Trouble working in children and adults:</u> • Self-reported • Difficulty conducting specific activities	**Statistical analysis:** • Linear regression models used • Models adjusted for race, sex, urban status, and income. **Results:** Change (standard error; SE) in outcome from the effect of residential optimal	No evidence of an effect of water fluoridation on general health, trouble working for children or adults, retardation in children.

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Participants: Child (14 to 15 years of age) and adult (17 to 90 years of age) civilians who are not institutionalized from the National Health and Nutrition Examination Survey III (NHANES III) **Sampling time frame:** NR **Sample size (N):** • Counties: 35 • Populations: > 500,000	• The same fluoridation exposure is given to all individuals in the same county **Exposure levels:** NR	(housework, gardening, exercise, or play) • Categories: No difficulty, some difficulty, moderate difficulty, and could not do <u>Retardation in children</u> • Self-reported • Physician diagnosed mental retardation <u>General Health in children and adults</u> • General health of participant as decided by physician • Categories: Excellent, very good, good, fair, and poor	water fluoridation among children • <u>Trouble working (N = 2,583)</u> β = 0.039 (0.039) • <u>Retardation (N = 4,796)</u> β = 0.001 (0.002) • <u>General Health (N = 4,618)</u> β = -0.159 (0.165) Change (SE) in outcome from the effect of optimal water fluoridation among adults • <u>Trouble working (N = 7,100)</u> β = 0.041 (0.043)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex: NR **Exclusions:** NR **Source of funding/ support:** NR **Author declaration of interest:** NR			• General health (N = 7,088) β = -0.028 (0.143)	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Study subject were from NHANES III where "national estimates of the health and nutritional status of the United States' civilian, noninstitutionalized population aged two months and older" are provided. Recruitment time frame not found.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Models adjusted for race, sex, urban status, and income
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable

Risk of bias assessment							
Attrition	Were outcome data complete without attrition or exclusion from analysis?	–	Not reported.				
Detection	Can we be confident in the exposure characterization?	++	Fluoride exposure estimated using data from the 1992 Fluoridation Census and 1990 Census from the US Bureau of the Census.				
	Can we be confident in the outcome assessment?	++	Trouble working is self-reported. Outcome assessors unlikely affected by exposure status as data were from different sources.	++	Retardation is self-reported. Outcome assessors unlikely affected by exposure status as data were from different sources.	++	General health status was determined by an examining physician. Outcome assessors unlikely affected by exposure status as data were from different sources.

Risk of bias assessment			
Selective reporting	Were all measured outcomes reported?	++	Yes, results were reported for general health, trouble working, and retardation.
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	+	Exposure was assessed at the level of the county. As individual levels of exposure were not measured, variation in fluoride levels within the county could not be accounted for in the analysis (i.e. potential difference in fluoride water exposure among those who drink tap water sometime compared to all the time).

Kousik 2016 [90]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:**	**Exposure:** <u>Fluoride levels in</u> • Urine samples • Ground water samples	**Outcomes:** • Body mass index (BMI) • Intelligence quotient (IQ)	**Statistical analysis:** • Correlation analysis **Results:**	• The results also reveal that exposure dose has a positive correlation with… urinary fluoride (r=0.513, P < 0.01), a negative correlation with IQ (r = −0.343,

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Cross-sectional study/ ecological study **Country:** India **Participants:** Children (6 to 18 years of age) from Simlapal Block in Bankura District **Sampling time frame:** NR **Sample size (N):** 149 **Sex:**	**Method of exposure assessment:** <u>Water samples</u> • Randomly acquired from 50 tube wells • Performed field investigations during November 2014 • Measured using ion-selective electrode • Used to calculate 'Fluoride exposure dose' (ED) which takes into consideration: Fluoride level Water intake/day Body weight <u>Urine samples</u>	**Method of outcome ascertainment:** <u>BMI</u> • Information needed for calculations were acquired from 8 primary schools <u>IQ</u> • Determined using the Combined Raven's Test for Rural China (CRT-RC) • Test was independently completed in a double-blind manner in the classroom • Scores were grouped as Retarded/low: ≤ 69 Borderline: 79 - 79 Below average: 80 – 89	• Correlation between urinary fluoride and exposure dose r = 0.513; p = <0.01 • Correlation between urinary fluoride and BMI r = 0.022; p not <0.01 • Correlation between urinary fluoride and IQ r = -0.751; p = <0.01 • Correlation between exposure dose and BMI r = -0.083; p not < 0.01 • Correlation between exposure dose and IQ r = -0.343; p = < 0.01 • Relationship between exposure dose and	P<0.01), and a non-significant correlation with BMI (r = 0.083). • Children residing in areas with higher than normal water fluoride level demonstrated more impaired development of intelligence

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
<u>Boys</u> • N = 66 **Exclusions:** NR **Source of funding/ support:** NR **Author declaration of interest:** NR	• Measured using ion-selective electrode **Exposure levels:** • Mean (SD) levels of fluoride <u>in water samples</u> 2.11 mg/L (1.64) • Levels of fluoride in urine samples Min = 0.45 mg/L Max = 17.00 mg/L	Average: 90 – 109 Above average: 110 – 119 Excellent: 120 – 129 Outstanding: ≥ 130	BMI among boys age 6-8 years BMI = 13.9 - 2.7 ED r = 0.073 p = 0.832 • Relationship between exposure dose and BMI among girls age 6-8 years BMI = 13.3 + 29.3 ED r = 0.092 p = 0.716 • Relationship between exposure dose and BMI among boys age 8-10 year BMI = 15.3 – 12.7 ED r = 0.124 p = 0.451 • Relationship between exposure dose and	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
			BMI among girls age 8-10 years BMI = 14.1 – 5.69 ED r = 0.144 p = 0.362 • Relationship between exposure dose and BMI among boys age >10 years BMI = 17.3 – 20.1 ED r = 0.217 p = 0.371 • Relationship between exposure dose and BMI among girls age >10 years BMI = 14.3 + 3.63 ED r = 0.133 p = 0.575	

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Participants consist of children (6 to 18 years of age) from Simlapal Block in Bankura District. Recruitment timeframe not found.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	–	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	No mention of excluding participants or missing data.

Risk of bias assessment					
Detection	Can we be confident in the exposure characterization?	++	Fluoride levels were measured in water and urine. No difference in assessment methods were reported between participants.		
	Can we be confident in the outcome assessment?	++	Eight primary schools of respective villages were used to collect … age, weight and height for calculating body mass index (BMI). Outcome unlikely to be affected by blinding status.	++	The intelligence quotient (IQ) of each child was measured according to Combined Raven's Test for Rural China (CRT-RC), published by Huadong Normal University in 1989. The children were administered to take the test in the classroom, working independently, in a double-blind manner according to the directions of the CRT-RC manual for the test administration conditions."
Selective reporting	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the abstract were reported on in the results section.		

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Risk of bias assessment			
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified.

Sabokseir 2016 [91]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:** Cross-sectional study **Country:**	**Exposures:** <u>Fluoride levels in</u> • Water **Method of exposure assessment:** • Acquired from the town's primary health care trust	**Outcome(s):** • Dental fluorosis **Method of outcome ascertainment:** • Dentists assessed photos using the Dean's Index and Thylstrup and Fejerskov (TF) Index	**Statistical analysis:** • Logistic regression was used to assess the association between fluoride drinking water levels and fluorosis **Results:**	• "Fluorosis indices, if used alone, could result in misdiagnosis of dental fluorosis and misguide health policymakers in their decision about public health measure related to use of fluoride."

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Iran **Participants:** Children (9 years of age) randomly selected from locations with high, optimal, and low fluoride drinking water levels in Fars **Sampling time frame:** NR **Sample size:** 376	**Exposure level:** Fluoride levels by town and category of exposure: <u>Gerash (high fluoride)</u> • 2.12 – 2.85 ppm <u>Sepidan (low fluoride)</u> • 0.24 – 0.29 ppm <u>Shiraz (optimal fluoride)</u> • 0.62 – 1.22 ppm		Percentage of genuine fluorosis by exposure categories • High Water Fluoride: 47.7% • Optimal Water Fluoride: 20.6% • Low Water Fluoride: 3.3% • p-value: <0.001 Odds (95% CI) of genuine fluorosis with optimal compared to high fluoride levels: • 0.292 (0.168 – 0.506) Odds (95% CI) of genuine fluorosis with low	• "Information about adverse health-related conditions linked to DDEs at specific positions on teeth could help to differentiate between genuine fluorosis and fluorosis-resembling defects." (p. 8)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Sex (N): Boys: 196 (53%) **Exclusions:** • Resided in other town from birth to age 5 years for >6 months • <7 permanent incisor teeth • Have orthodontic brackets • Have overlapping teeth • Have large restorations • Have severe extrinsic stains on incisors **Source of funding / support:** • Vice-Chancellery for Research of Shiraz University of Medical Science			compared to high fluoride levels: • 0.037 (0.011 – 0.127)	

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Author declaration of interest: No COI				

Risk of bias assessment			
Bias domain	***Criterion***	***Response***	
Selection	Was administered dose or exposure level adequately randomized?	N/A	Not applicable
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	+	Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	Study accounted only for sex

Risk of bias assessment			
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (resided in other town from birth to age 5 years for >6 months, have <7 permanent incisor teeth, orthodontic brackets, overlapping teeth, large restorations, or severe extrinsic stains on incisors).
Detection	Can we be confident in the exposure characterization?	++	Yes, fluoride exposure levels were obtained from each town's primary health care trust records
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was measured by 8 calibrated dentists: 4 using the Dean's Index (DI) and 4 using Thylstrup and Fejerskov (TF) Index. The diagnosis of dental fluorosis was confirmed only if three out of four dentists of each group agreed. Dentists were blinded to participants' clinical condition and residence.

Risk of bias assessment			
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Xiang 2016 [92]

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Reference type: Original study **Study design:**	**Exposures:** Fluoride levels in • Taps, deep wells, or river sources	**Outcome(s):** • Dental fluorosis • Defect dental fluorosis	**Statistical analysis:** • Prevalence of dental fluorosis and defect dental fluorosis were calculated	"This study suggests that defluoridation of drinking water is effective for

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Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Cross-sectional study **Country:** China **Participants:** Children (8 – 14 years of age) from Wamiao and Xinhuai **Sampling time frame:** • 2002: before defluoridation • 2013: 10 years after defluoridation **Sample size (N):**	**Method of exposure assessment:** • Fluoride ion selective electrode **Exposure level:** Mean fluoride level in tap water (SD) in 2013 <u>Wamiao</u> • 0.91 mg/L (0.02) <u>Xinhuai</u> 0.89 mg/L (0.03)	**Method of outcome ascertainment:** • Permanent teeth were examined by dentists and endemic fluorosis control and prevention expert • Assessment conducted using Dean's classification and the Chinese "Clinical diagnostic standard for dental fluorosis" Defect dental fluorosis: "Defect means there was a small dent, or/and a large pit, or/and a larger striped area in the surface of the dental enamel. Defect dental fluorosis included some "moderate" dental	**Results:** • **"**The prevalence of dental fluorosis and defect dental fluorosis in 2002 had a significant positive dose–response correlation with the drinking water fluoride with the coefficient correlations, regression equations, and p values being r=0.999, y=99.552/(1+40.049×e–3.464x), and p=0.017; and r=0.987, y=17.520x – 6.950, and p=0.001, respectively." (p. 23) • "The prevalence of dental fluorosis and defect dental fluorosis were significantly decreased with the decreased drinking water fluoride in Wamiao in 2013 after defluoridation compared with the results in 2002." (p. 23)	controlling endemic fluorosis in China and that the role of fluoridation of public water supplies for the of control dental caries needs to be further studied." (p. 23)

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
2002: • Wamiao = 236 • Xinhuai = 290 2013: • Wamiao = 68 • Xinhuai = 65 **Sex (N):** Wamiao in 2002 Men: 130 (55.1%) Xinhuai in 2002 Men: 159 (54.8%) **Exclusions:** 2013 participants		fluorosis (grade 3) and all “severe” dental fluorosis (grade 4) as diagnosed by Dean’s criteria” (p. 25)		

Study Characteristics				
Study	**Exposure**	**Outcome**	**Analysis & Results**	**Conclusions**
Absent from village for >=1year **Source of funding / support:** National Natural Science Foundation of China **Author declaration of interest:** No COI				

Risk of bias assessment		
Bias domain	***Criterion***	***Response***
Selection	Was administered dose or exposure level adequately randomized?	N/A Not applicable

Risk of bias assessment			
	Was allocation to study groups adequately concealed?	N/A	Not applicable
	Did selection of study participants result in appropriate comparison groups?	++	Yes, participants were selected during the same timeframe and according to the same criteria.
Confounding	Did the study design or analysis account for important confounding and modifying variables?	-	NR
Performance	Were experimental conditions identical across study groups?	N/A	Not applicable
	Were the research personnel and human subjects blinded to the study group during the study?	N/A	Not applicable
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	Study provided reasons for exclusion of participants (those who were absent from village for >=1year).
Detection	Can we be confident in the exposure characterization?	++	Yes, exposure was measured in water using a fluoride ion selective electrode (Manufactured by Chang Sha Yi Ming Experimental Instrument Co., Ltd, China).
	Can we be confident in the outcome assessment?	++	Yes, outcome (dental fluorosis) was assessed by 2 dentists and 1 expert in endemic fluorosis using Dean's Index and the Chinese "Clinical diagnostic standard for

Risk of bias assessment			
			dental fluorosis" (WS/T208-2001). Lack of blinding of outcome assessors would not appreciably bias results.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail for data extraction
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

2.3. Quality assessment of the included human studies[xxx]

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Mercado 2023 [6]	N/A	N/A	++	–	N/A	N/A	++	++	++	++	++	2
Tang 2023 [7]	N/A	N/A	+	++	N/A	N/A	++	++	++	++	++	2
Ahmad 2022 [8]	NA	NA	–	–	N/A	N/A	–	–	–	++	++	3
Feng 2022 [9]	N/A	N/A	++	++	N/A	N/A	++	++	–	++	++	2
García-Escobar 2022 [10]	NA	NA	+	–	NA	NA	++	++	++	++	++	2
Goodman 2022 [11]	N/A	N/A	+	++	N/A	N/A	++	++	++	++	++	1
Gupta 2022 [12]	N/A	N/A	++	–	N/A	N/A	++	++	– –	++	++	2
Ibarluzea 2022 [13]	NA	NA	++	++	NA	NA	++	++	++ ++	++	++	1
Kaur 2022 [14]	N/A	NA	++	–	NA	NA	++	++	+	++	++	2

[xxx] Quality of evidence was assessed using the OHAT risk of bias tool

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Marques 2022 [15]	NA	NA	++	++	NA	NA	++	++	++	++	++	1
McLaren 2022 [16]	NA	NA	++	++	NA	NA	++	+	++	++	++	1
Rani 2022 [17]	NA	NA	+	–	NA	NA	–	++	++	++	++	2
Saeed 2022 [18]	N/A	N/A	+	++	N/A	N/A	–	++	+ ++	++	++	2
Tawfik 2022 [19]	N/A	N/A	++	–	N/A	N/A	++	+	++	++	++	2
Thilakarathne 2022 [20]	NA	NA	+	–	NA	NA	++	++	++	++	++	2
Al-Omoush 2021 [21]	N/A	N/A	+	–	N/A	N/A	–	++	++ ++	++	2	2
Ayele 2021 [22]	N/A	N/A	++	+	N/A	N/A	++	++	++ –	++	++	2
Cao 2021 [23]	N/A	N/A	++	–	N/A	N/A	–	++	++	++	++	2
Dong 2021 [24]	N/A	N/A	++	++	N/A	N/A	–	++	++	++	++	1
Du 2021 [25]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Farmus 2021 [26]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Fernandes 2021 [27]	NA	NA	++	–	NA	NA	++	++	++	++	++	2
Helte 2021 [28]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
James 2021 [29]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Meghe 2021 [30]	N/A	N/A	+	–	N/A	N/A	+	++	–	++	++	2
Meng 2021 [31]	N/A	N/A	++	–	N/A	N/A	–	++	++	++	++	2
Mohd Nor 2021 [32]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Rojanaworarit 2021 [33]	NA	NA	++	++	NA	NA	++	++	++	++	++	1
Sharma 2021 [34]	N/A	N/A	+	–	N/A	N/A	–	++	–	++	++	2
Silva 2021 [35]	N/A	N/A	+	++	N/A	N/A	++	++	++	++	++	1
Tkachenk 2021 [36]	N/A	N/A	+	–	N/A	N/A	++	+	++	++	++	2
Wang 2021 [37]	N/A	N/A	++	++	N/A	N/A	++	++	++ ++	++	++	1
Yani 2021 [38]	N/A	N/A	+	–	N/A	N/A	++	–	+ +	++	++	2

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Yu 2021 [39]	N/A	N/A	++	++	N/A	N/A	++	++	+	++	++	1
Zhao 2021 [40]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Bai 2020 [41]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Cui 2020 [42]	N/A	N/A	++	–	N/A	N/A	++	++	+ ++ ++	++	++	2[xxxi]
Das 2020 [43]	N/A	N/A	++	–	N/A	N/A	–	++	++	++	++	2
Fernandes 2020 [44]	N/A	N/A	+	–	N/A	N/A	++	++	++	++	++	2
Godebo 2020 [45]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Kim 2020 [46]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Krishna 2020 [47]	N/A	N/A	++	+	N/A	N/A	++	++	++	++	++	1
Lee 2020 [48]	N/A	N/A	++	+	N/A	N/A	++	++	++	++	++	1

[xxxi] *Cui 2020: Assessment of question 9 (Outcome assessment) was (+) for IQ and (++) for thyroid dysfunction and dopamine outcomes. However, the overall study assessment did not change due to this difference.*

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Nanayakkara 2020 [49]	N/A	N/A	+	–	N/A	N/A	–	++	++	++	++	2
Russ 2020 [50]	N/A	N/A	++	+	N/A	N/A	++	++	++	++	++	1
Stangvaltaite-Mouhat 2020 [51]	N/A	N/A	+	–	N/A	N/A	–	++	++	++	++	2
Sun 2020 [52]	N/A	N/A	+	++	N/A	N/A	++	++	++	++	++	1
Till 2020 [53]	N/A	N/A	++	++	N/A	N/A	++	+	++	++	+	1
Wang 2020 [54]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
An 2019 [55]	N/A	N/A	++	+	N/A	N/A	++	++	++	++	++	1
Crnosija 2019 [56]	N/A	N/A	++	– –	N/A	N/A	++	– –	++	++	++	2
Fernando 2019 [57]	N/A	N/A	–	– –	N/A	N/A	++	++	+	++	– –	2
Jimenez-Cordova 2019 [58]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Jimenez-Cordova 2019a [59]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Khanoranga 2019 [60]	N/A	N/A	++	–	N/A	N/A	–	++	++	++	++	2
Liu 2019 [61]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Malin 2019 [62]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Malin 2019a [63]	N/A	N/A	++	++	N/A	N/A	++	+	++	++	++	1
Pei 2019 [64]	N/A	N/A	+	– –	N/A	N/A	++	++	++	++	++	2
Riddell 2019 [65]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Shaik 2019 [66]	N/A	N/A	+	– –	N/A	N/A	++	++	++	++	++	2
Soto-barreras 2019 [67]	N/A	N/A	++	–	N/A	N/A	++	++	++	++	++	2
Zhang 2019 [68]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Zhou 2019 [69]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Zhou 2019a [70]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Bashash 2018 [71]	N/A	N/A	++	++	N/A	N/A	++	++	+ ++	++	++	1[xxxii]
Cui 2018 [72]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Jimenez-Cordova 2018 [73]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Kumar, V 2018 [74]	N/A	N/A	+	–	N/A	N/A	++	++	++	++	++	2
Kumar, S 2018 [75]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Malin 2018 [76]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Mohd Nor 2018 [77]	N/A	N/A	++	–	N/A	N/A	++	++	++	++	++	2
Mustafa 2018 [78]	N/A	N/A	+	–	N/A	N/A	++	++	++	++	+	2

[xxxii] *Bashash 2018: Assessment of question 9 (outcome assessment) was different for both outcomes. However, the overall study assessment did not change due to this difference.*

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Oweis 2018 [79]	N/A	N/A	++	++	N/A	N/A	++	–	++	++	++	2
Quadri 2018 [80]	N/A	N/A	++	–	N/A	N/A	–	++	+	+	+	2
Rathore 2018 [81]	N/A	N/A	+	–	N/A	N/A	++	++	++	++	+	2
Shruthi 2018 [82]	N/A	N/A	++	–	N/A	N/A	++	++	–	++	++	2
Yu 2018 [83]	N/A	N/A	++	++	N/A	N/A	++	++	++	++	++	1
Arulkumar 2017 [84]	N/A	N/A	+	–	N/A	N/A	++	++	++	++	++	2
Bashash 2017 [85]	N/A	N/A	++	+	N/A	N/A	–	+	++	++	++	1
Chauhan 2017 [4]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Stephenson 2017 [5]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Verma 2017 [86]	N/A	N/A	++	++	N/A	N/A	–	++	++	++	++	1
Cardenas-Gonzalez 2016 [87]	N/A	N/A	++	++	N/A	N/A	++	++	++	+	++	1
de Moura 2016 [88]	N/A	N/A	++	–	N/A	N/A	++	–	++	++	++	2

Study	Selection bias			Confounding bias	Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other sources of bias	Overall quality of evidence (Score)
	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Other potential threats to internal validity	
Heck 2016 [89]	N/A	N/A	+	+	N/A	N/A	–	++	++	++	+	1
Kousik 2016 [90]	N/A	N/A	+	–	N/A	N/A	++	++	++	++	++	2
Sabokseir 2016 [91]	N/A	N/A	+	+	N/A	N/A	++	++	++	++	++	1
Xiang 2016 [92]	N/A	N/A	++	–	N/A	N/A	++	++	++	++	++	2

Assessment criteria

Key criterion *Other (non-key) criterion*

Level of bias

DL: *definitely low risk of bias* ++ ***PL:*** *probably low risk of bias* + ***PH:*** *probably high risk of bias* – ***DH:*** *definitely high risk of bias* – –

Table 1: Summary of eligible reviews of human evidence[xxxiii]

Reference ***(Study Design)***	**Comprehensiveness**	**Methodological Rigor**	**Summary of Author-reported conclusions**
Grandjean 2019 [94] *(Literature Review)*	**Time Period Covered by Search** • Restricted to most recent 10 years **Sources Searched** • Electronic databases (Pubmed) • Grey literature (Yes) • Reference list of articles (Yes) **Number of References Included** • N= 14 cross-sectional studies • N= 5 prospective studies • N= 2 retrospective studies	**Was screening conducted by two independent reviewers?** • NR **Was data abstraction conducted by two independent investigators?** • NR **Was quality assessment conducted by two independent investigators?** • NR	The recent epidemiological results support the notion that elevated fluoride intake during early development can result in IQ deficits that may be considerable. Recognition of neurotoxic risks is necessary when determining the safety of fluoride-contaminated drinking water and fluoride uses for preventive dentistry purposes.
Saeed 2019 [95] *(Literature Review)*	**Time Period Covered by Search** • 1989 to 2019 **Sources Searched** • Electronic databases	**Was screening conducted by two independent reviewers?** • NR	The significant downsides of fluoride outweigh its benefits for dental problems across many endemic areas of the world. The findings in past literature studies are alarming and the seriousness of this debate urges expediting policymaking and

[xxxiii] Information and data in this table was taken directly from the original publications

Reference *(Study Design)*	Comprehensiveness	Methodological Rigor	Summary of Author-reported conclusions
	(PubMed, Environmental Health Perspectives, MEDLINE, Google Scholar, Fluoride Action Network, Elsevier, and Springer) • Grey literature (NR) • Reference list of articles (NR) **Number of References Included** N= 57	**Was data abstraction conducted by two independent investigators?** • NR **Was quality assessment conducted by two independent investigators?** • NA	awareness campaigns for public safety. The current review highlights some gaps in past literature, needing to be bridged in future research on fluoride toxicity among the human population. The review also prompts the need for more research work on school-going children to curb the rise of dental and skeletal fluorosis and mental disabilities related to early childhood exposure to fluoride in developing countries.
Chaitanya 2018 [96] *(Systematic Review)*	**Time Period Covered by Search** • January 1981 to November 2015 **Sources Searched** • Electronic databases (PubMed, Medline, Embase, Cochrane Library, EBSCO) • Grey literature (NR) • Reference list of articles (NR) **Number of references included**	**Was screening conducted by two independent reviewers?** • No **Was data abstraction conducted by two independent investigators?** • No **Was quality assessment conducted by two independent investigators?** • NA	The present systematic review suggests a positive correlation between excess fluoride and hypothyroidism. This calls the need for further well-controlled studies in this otherwise emerging alarming issue. It also calls for considerable community network through health informatics for problem sensitization.

Reference *(Study Design)*	Comprehensiveness	Methodological Rigor	Summary of Author-reported conclusions
	• N= 10		
Duan 2018 [97] *(Meta-analysis)*	**Time Period Covered by Search** • Electronic databases searched throughout November 2016 **Sources Searched** • Electronic databases (PubMed, Embase, and Cochrane Library) • Grey literature (NR) • Reference list of articles (Yes) **Number of References Included** N= 26	**Was screening conducted by two independent reviewers?** • Yes **Was data abstraction conducted by two independent investigators?** • Yes **Was quality assessment conducted by two independent investigators?** • Yes	Greater exposure to high levels of fluoride in water was significantly associated with reduced levels of intelligence in children. Therefore, water quality and exposure to fluoride in water should be controlled in areas with high fluoride levels in water.
PHO 2018 [98] *(Literature Review)*	**Time Period Covered by Search** • January 1, 2009 – May 10, 2017 **Sources Searched** • Electronic databases (Ovid MEDLINE, Embase, CINAHL, and Dentistry)	**Was screening conducted by two independent reviewers?** • NR **Was data abstraction conducted by two independent reviewers?** • NR	• Outcomes include dental fluorosis, enamel opacities, hypo-mineralization, and bone health, cancers including bone cancers, reproductive, neurobehavioral effects, mutagenicity, hypothyroidism, and urolithiasis.

Reference *(Study Design)*	Comprehensiveness	Methodological Rigor	Summary of Author-reported conclusions
	• Grey literature (Yes) • Reference list of articles (NR) **Number of References Included** • N= 29 articles (Systematic reviews N= 2; cross-sectional studies N= 20; prospective cohort studies N= 5; case-control studies N= 2) • N= 6 documents from grey literature search	**Was quality assessment conducted by two independent investigators?** • NR	• Overall, the existing literature suggests that at an optimal concentration of water fluoridation, the only adverse health consequence observed is a mild form of dental fluorosis. • The 2010 Health Canada fluoride document states that there is no evidence to support a link between exposure to fluoride in drinking water at or below 1.5 mg/L and any adverse health effects such as any types of cancer, developmental defects, neurobehavioral effects, or genotoxicity. The studies conducted and the organizational reports published after the 2010 Health Canada fluoride document and until May 10, 2017 corroborate these findings.

NR = Not Reported; NA = Not Applicable

2.4. Overview of human evidence

Out of a total of 38 endpoints reported in the current review, the current literature search identified new human evidence relating to 15 endpoints, which were not reported in either NHMRC [99, 100] or CADTH [2, 3] reports. CADTH had initially reported on 23 endpoints, for which the current review updated the evidence on 14 of those endpoints and found no new evidence on the remaining 9 endpoints. This section describes the evolving evidence reported in NHMRC 2016, CADTH 2019, and the current updated review of the literature. A summary is provided for all endpoints in the main manuscript. Where no earlier evidence was reported, the CADTH 2019 conclusion was described as 'N/A'. While no limit was used to restrict studies based on fluoride exposure levels as an exclusion criterion for the literature review, synthesis of evidence was predominantly based on studies generally relevant to the North American context. Although these studies may involve fluoride water concentration higher than those in North American drinking water supplies, they are relevant to the evaluation of causality and exposure-response assessment. Some studies reported results based on serum/urinary fluoride levels). Where available, fluoride levels in drinking water were listed in the following section for the purpose of comparison across studies.

All-cause mortality

NHMRC 2016 [99, 100] identified one major study with acceptable quality that reported a small decrease in all-cause mortality incidence in association with CWF. No further evidence was identified by CADTH 2019 [2] or Current literature search in relation to all-cause mortality.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and all-cause mortality.

Bone health

Bone cancer

NHMRC [99, 100] identified three studies of acceptable quality and three of low quality, where all except one of low quality concluded no association between water fluoridation and bone cancer. NHMRC also identified two systematic reviews where one reported a positive association only in males, and

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the other reported no clear association. CADTH 2019 [2] identified two further studies of acceptable quality, and reported that the evidence up to that date was largely in support of no association between fluoride and bone cancer. The current literature search identified 1 case control study [46] and 2 ecological studies [48, 56] of high/acceptable quality that were conducted in South Korea [48], and the US [46, 56]. Two of these studies concluded the absence of association between bone cancer and water fluoridation at a fluoride exposure range between 0.04-0.8 ppm [46, 56]. The third study [48] that concluded the absence of association did not report a water fluoride exposure level.

Current review evidence synthesis: Based on the available literature to date, there is consistent evidence of no association between bone cancer and fluoride exposures relevant to current North American drinking water levels.

Bone density and quality

NHMRC 2016 [99, 100] identified one systematic review and one study of low quality, which concluded the absence of association between bone quality or osteoporosis (low mineral bone density) and exposure to fluoride. No further evidence was identified by CADTH 2019 [2]. The current literature search identified 5 new studies including 4 studies of high quality [28, 45, 48, 52] and a fifth study with acceptable quality [79]. One cohort study from Sweden [28] and 2 cross-sectional studies from China [52] and Ethiopia [45] concluded a positive association between bone quality disruption and fluoride in drinking water (≤1 ppm) [28] or ground water (6.8 ppm) [45]. The Chinese study [52] did not report on the examined fluoride exposure level. Alternatively, 2 studies reported no association between fluoride exposure/intake and bone quality disruption. One ecological study was conducted in South Korea [48] on residents from all ages (no water fluoride level reported). Another US cohort study [79] was conducted on adolescents (17 years of age) and reported no association between bone quality disruption and life-long fluoride intake from all sources (0.7-0.9 ppm) [79].

Current review evidence synthesis: Based on the available literature to date, there is inconsistent evidence for the association of bone quality and fluoride exposures relevant to current North American drinking water levels.

Bone, hip fracture

NHMRC 2016 [99, 100] reported two systematic reviews and two studies of acceptable quality, which showed no clear association between fluoride and hip fractures. The later review by CADTH 2019 [2] identified one additional study of acceptable quality and concluded that evidence was consistent for no association with fluoride exposure. The current literature search identified 1 ecological study [48] of high quality that was conducted in South Korea and concluded the absence of an association between fluoride exposure and the risk of hip fracture.

Current review evidence synthesis: Based on the available literature to date, there is consistent evidence of no association between hip fracture and fluoride exposures relevant to current North American drinking water levels

Bone, musculoskeletal pain

NHMRC 2016 [99, 100] identified two studies of low quality, which reported a positive association between musculoskeletal pain and higher fluoride levels (not applicable to the North American context). No further evidence was identified by CADTH 2019 [2] or in the current updated literature review in relation to musculoskeletal pain.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and musculoskeletal pain.

Cancer, total incidence and mortality

The earlier review by NHMRC 2016 [99, 100] reported conflicting evidence for the association of cancer incidence and mortality based on examination of two systematic reviews and three individual studies of acceptable quality. CADTH 2019 [2] identified an additional study of acceptable quality that reported an inverse association and concluded that there was consistent evidence of no association. The current literature search did not identify any new evidence relating to cancer incidence and mortality.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Consistent evidence for no association between water fluoridation at current North American levels and the overall incidence of cancer or cancer-related mortality.

Trial Ex. 131.628

Cognition

Cognition, ADHD

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019a [3] that reported on the association of fluoride with ADHD. The current literature search identified two studies of high quality which examined the association between fluoride exposure and ADHD in youth [65] and in children due to maternal exposure to fluoride during pregnancy [71]. The first one [65] was a cross-sectional study conducted on North American youth 6-17 years old from the North American Health Measures Survey (Cycles 2 and 3). The study reported a significantly positive association between tap water fluoride (mean of 0.04 mg/L in non-fluoridated regions to 0.49 mg/L in fluoridated regions) and the risk of ADHD including symptoms of hyperactivity and inattention, especially among adolescents. The second study [71] was a cohort study conducted in Mexico, which enlisted 213 mother-child pairs as part of the ELEMENT study. This study reported an association between higher maternal fluoride levels (measured during pregnancy, mean MUFcr was 0.85 mg/L (SD=0.33)) and "more behavioral symptoms of inattention, but not hyperactivity or impulse control" measured in the children at 6-12 years old. In the study, water fluoride levels of 0.15-1.38 ppm were extrapolated from an earlier study on the ELEMENT cohort in 2017 [85].

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of ADHD and fluoride exposures relevant to current North American drinking water levels.

Cognition, dementia

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019a [3] that reported on the association of fluoride with dementia. The current literature search identified one large, high quality cohort study [50] that was conducted in Scotland and included all people born in 1921 who were at school in Scotland in June 1932, and took part in a comprehensive national intelligence test at a mean age of 11 years (Scottish Mental Survey 1932, SMS1932). The study reported a positive association between the risk of dementia and higher fluoride levels in men and women who consumed water with low fluoride levels (0.05 ppm).

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of dementia and fluoride exposures relevant to current North American drinking water levels.

Cognition, Down syndrome

NHMRC 2016 [99, 100] reported on two systematic reviews which did not show a clear association between fluoride and Down syndrome, compared to another study with an large population size and acceptable quality that showed no such association. CADTH 2019a [3] identified an additional, large-size observational study with acceptable quality that reported no association of fluoride exposure and Down syndrome. The current literature search did not identify any new evidence relating to Down syndrome.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Limited evidence for no association between water fluoridation at current North American levels and Down syndrome.

Cognition, IQ

Based on one systematic review and eleven studies (1 high, 2 acceptable, and 8 low quality), the NHMRC [99, 100] reported mixed findings regarding the association of fluoride exposure with lower IQ scores in children. A subsequent report by [3] identified a North American cohort study [101] that used data from the MIREC birth cohort, which was conducted on mother-child pairs from six major North American cities. The study reported a positive association between maternal exposure to fluoride and reduction of IQ levels in children 3-4 years old. Despite describing the evidence as weak based on this single cohort study, [3] suggested that results should be part of the efforts to further explore the possible association of fluoride exposure and neurological development in children. In a 2020 update to their 2019 review of neurological and cognitive effects, [102] identified two additional studies of low quality in relation to IQ, and concluded there was insufficient evidence for an association between IQ levels and “fluoride exposure at the North American water fluoride levels (optimum at 0.7 mg/L)” .

A 2020 draft report[xxxiv] [103] by the US National Toxicology Program (NTP) concluded that exposure to fluoride *"is presumed to be a cognitive neurodevelopmental hazard"* in children, with only limited evidence in support of cognitive effects in adults. This statement was modified in 2022 [104] in response to another NASEM review: "This review finds, with moderate confidence, that higher fluoride exposure (e.g., represented by populations whose total fluoride exposure approximates or exceeds the World Health Organization Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride) is consistently associated with lower IQ in children. More studies are needed to fully understand the potential for lower fluoride exposure to affect children's IQ." According to NTP, for effects on children's IQ at exposure levels below 1.5 mg/L, the supporting studies provided less consistent results and were mostly at higher risk of bias.

The current literature search identified 21 studies including 13 studies of high quality [11, 13, 18, 26, 37, 39, 40, 53, 54, 72, 78, 83, 85], and 5 studies of moderate quality [9, 14, 38, 78, 90] that reported a positive/possible association between fluoride exposure and reduced IQ scores and school performance in children. Three studies of high [89], moderate [67], or low [8] quality reported an absence of association with reducing IQ scores.

Studies reporting positive association include a recent and high-quality analysis of critical time windows of exposure using the North American MIREC cohort [26], which reported an association between children's performance IQ and fluoride exposure during the perinatal period and into early childhood. Results suggest that prenatal exposure may be more critical for effects in boys but infancy (over the first year) as the more critical exposure window for girls [409]. An earlier study that used the same cohort [53] reported that an increment of 0.5 mg/L in water fluoride concentration corresponded to a 9.3- and a 6.2-point reduction in performance IQ in formula-fed and breastfed children, respectively. Such an association remained significant upon controlling for fetal fluoride exposure.

[xxxiv] NTP disclaimer: This DRAFT Monograph is distributed solely for the purpose of pre-dissemination peer review under the applicable information quality guidelines. It has not been formally disseminated by NTP. It does not represent and should not be construed to represent any NTP determination or policy. The September 6, 2019 draft monograph was peer reviewed by a committee convened by the National Academy of Sciences, Engineering, and Medicine (NASEM). This current draft incorporates changes in response to that review and is being submitted to the same NASEM committee for an additional round of peer review.

Results from a recent study [11] that used data from the Mexican Cohort ELEMENT suggested that maternal urinary fluoride exposure may affect visual-spatial and perceptual cognitive domains more so than verbal. The study reported a drop of 2 points in IQ scores for each 0.5 mg/L increase in maternal urinary fluoride. An earlier, high quality study [85] that analyzed the same Mexican cohort reported a positive association of maternal exposure to fluoride during pregnancy with lower GCI (IQ) scores in children at approximately 4 years old, and with lower Full-Scale IQ scores at 6–12 years old. A fifth study [13] examined prenatal fluoride exposure in a small mother-child birth cohort in Spain: Results in boys suggest improved scores in cognitive domains with maternal urinary concentrations.

In a 2020 study [54] reported a significant IQ score reduction for each 1 mg/L increase in water fluoride concentration [β: −1.59 (−2.61, −0.57), p=0.002]. An earlier study by [83] reported that each increment of 0.5 mg/L in water fluoride corresponds to a 40% reduction in the odds of having excellent IQ in those exposed to low fluoride levels (0.20-1.40 mg/L). Another high quality study [72] reported an association with reduced IQ scores only in children carrying the dopamine receptor-2 (DRD2) Taq 1A- TT genotype, with no similar association with the other DRD2 Taq 1A genotypes. And finally, a cross-sectional study conducted by [90] reported a positive and significant correlation between exposure dose and IQ reduction ($r = -0.343$, $p < 0.01$).

These studies reported a reduction of IQ scores in association with water fluoride concentrations of 0.01-2.07 ppm [78], 0.58 ppm [53], 0.1–1.6 ppm [38], 0.15-1.38 ppm [85], 0.1–15.8 ppm [18], 0.20–2.49 ppm [72], 0.20–3.90 ppm[37], >1.0 ppm [9],1.39 ppm [54], 1.53–2.84 ppm [40], 2.0 ppm [83], 2.11 ppm [90], 2–5 ppm [14]. Three studies with acceptable quality reported no effect of fluoride on children's IQ at fluoride exposures of 0.3-3.0 ppm [89], 1.22 ppm ±1.09 [67] or 2.04 ppm [8].

Current review evidence synthesis: Based on the available literature to date, the accumulating body of evidence suggests a positive association of reduced IQ scores for children and fluoride exposures relevant to current North American drinking water levels.

Cognition, trouble working

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019a [3] that reported on the association of fluoride with memory loss. The current literature search identified a large cross-sectional study [89] with acceptable quality that was conducted using data on >500,000 US
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adolescents and adults from the National Health and Nutrition Examination Survey III (NHANES III). The study reported no association between exposure to water fluoride (0.3-3 ppm) and trouble working.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of trouble working and fluoride exposures relevant to current North American drinking water levels.

Cardiovascular diseases (CVD)

A number of studies examining individual cardiovascular endpoints were reported in earlier reviews [2, 99] as well as by the current review. Whereas the evidence for each individual endpoint is supported by few studies, and given the fact that these endpoints are closely interrelated, the evolving evidence merits further investigation to properly assess the association of fluoride exposure with cardiovascular diseases.

CVD, atherosclerosis

Based on a single study with low quality, NHMRC 2016 [99, 100] reported a significantly higher risk of carotid artery atherosclerosis in adults in areas with high fluoride levels (>1.2 ppm). No further studies were identified by CADTH 2019 [2]. The current literature review identified 3 additional studies that examined the association of fluoride with cardiovascular disease biomarkers. A cross-sectional study [36] with acceptable quality in Ukraine reported that children in the fluorosis area (>1.5 ppm) showed higher blood TBARS levels, while the acyl hydroperoxide levels were non-significantly increased in comparison with healthy children living in the non-fluorosis area. Another cross-sectional study with high quality [58] that was conducted in 2015 on 5-12 years old Mexican school children. The study reported significant association of fluoride exposure (0.3 ppm) with alterations in some cardiovascular disease biomarkers, suggesting fluoride exposure may be atherogenic and may increase the likelihood of cardiovascular diseases later in life. A third study of case-control design with acceptable quality [84] was conducted on patients with dental and skeletal fluorosis in India. The study reported variable associations of fluoride (>1.5 ppm) with different cardiovascular disease biomarkers, which support the chances of cardiovascular-related complications in fluorosis patients.

Current review evidence synthesis: Based on the available literature to date, there is limited evidence for an association of atherosclerosis and fluoride exposures relevant to current North American drinking water levels.

CVD, hypertension

Five studies were reported by NHMRC 2016 [99, 100] (n=3) and CADTH 2019 [2] (n=2) provided mixed findings on the association of fluoride with risk of hypertension. All studies were of low quality and were derived from countries with higher fluoride levels compared to those implemented in Canada. The current review did not identify any additional studies in relation to this endpoint.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and hypertension.

CVD, myocardial infarction

There were no earlier studies identified in NHMRC 2016 [99, 100]. With only one study with large population size and low quality that reported no association between fluoride and myocardial infarction, CADTH 2019 [2] concluded there was insufficient evidence for this association. The current review did not identify any additional studies in relation to myocardial infarction.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and myocardial infarction.

Diabetes mellitus

As reported by CADTH 2019 [2], there were only two earlier studies with low quality that provided mixed evidence for the association of exposure to fluoride with risk of diabetes mellitus (DM). No earlier studies were identified by NHMRC 2016 [99, 100]. The current literature search identified 1 study of high quality that was conducted in India and concluded that the increase in serum Fluoride

increases diabetes mellitus and diabetic nephropathy [47]. Serum fluoride levels ranged from 0.5128 ±0.30 (DM with CKD) to 0.6318 ±0.59 (DM without CKD).

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of diabetes mellitus and fluoride exposures relevant to current North American drinking water levels.

Eye diseases and conditions

Eye, select diseases

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride with eye diseases. The current review identified one study [69] of high quality that was conducted on Chinese adults aged ≥40 years old, with no congenital eye disease or ocular trauma, for examining the association between water fluoride exposure (>1.2 ppm) and seven eye diseases. The study reported significant positive associations with pterygium and arteriosclerotic retinopathy, a significant inverse association with cataracts, and non-significant associations with primary angle closure glaucoma, diabetic retinopathy, age-related macular degeneration, and strabismus.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of any of the examined eye diseases and fluoride exposures relevant to current North American drinking water levels.

Eye, refractive errors

An earlier review by CADTH 2019 [2] identified a single low-quality study and concluded that evidence was insufficient for an assessment of this association. There were no earlier studies identified in NHMRC 2016 [99, 100] or Current literature search in relation to the association of fluoride exposure with the prevalence of refractive errors (myopia, hyperopia, astigmatism) [2].

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and refractory errors.

Fluorosis

Fluorosis, dental

Earlier evidence on the association of fluoride with dental fluorosis was reported by NHMRC [99, 100] (three systematic reviews) and CADTH [2] (21 studies: 1 acceptable, 19 low; N= 35,374), which reported consistent findings for an association between fluoride and dental fluorosis. The current literature search identified 33 cross-sectional studies, including 15 studies of high quality [15, 18, 19, 23, 24, 29, 32, 33, 35, 37, 70, 75, 86, 91, 105] and 18 studies of acceptable quality [6, 7, 10, 12, 17, 20, 21, 27, 34, 38, 43, 44, 51, 60, 67, 77, 88, 92] that were not included in earlier reviews. Thirty-two of those studies reported a positive/possible association with dental fluorosis at a wide range of fluoride concentration in drinking water (both tap and ground). Out of those 32 studies, 6 were conducted in China [7, 17, 23, 37, 70, 92], 5 in India [10, 12, 34, 75, 86], 5 in Brazil [15, 27, 35, 44, 88], 2 in Malaysia [32, 77], 2 in Pakistan [18, 60], and 1 in each of Canada [105], Egypt [19], Indonesia [38], Iran [91], Jordan [21], Lithuania [51], Mexico [67], Peru [6], Saudi Arabia [43], Sri Lanka [20], Thailand [33], and USA [24].

The study by [24] included children and adolescents (age 6 to 19 years), and reported the odds (95%CI) of dental fluorosis (Dean's Fluorosis Index (DFI) ≥1) as 1.48 (1.13, 1.96), 1.92 (1.44, 2.58), and 2.30 (1.75, 3.07) times greater at water fluoride levels of 0.31 – 0.50 mg/L, 0.51 – 0.70 mg/L, and >0.70 mg/L, compared to ≤0.30 mg/L. [32] conducted a study on children (age 9 to 12 years) and reported that compared to those exposed to non-fluoridated water, the odds of dental fluorosis (DFI ≥ 2) (95% CI) were 5.97 (3.32, 10.72) times greater among children with a lifetime exposure to 0.5 ppm fluoride, and 9.12 (5.15, 16.14) times greater among those exposed to 0.7 ppm fluoride during the first two years of life, followed by a level of 0.5 ppm.

The study by [70] included children (age 7 to 13 years) from rural areas with low-to-moderate levels of fluoride and reported that each 1mg/L increase of water fluoride was associated with a 1.47 (1.40, 1.55), 1.85 (1.63, 2.11), 1.68 (1.57, 1.79), and 3.85 (3.01, 4.92) increased odds (95% CI) of total, very mild, mild and moderate dental fluorosis, respectively [70]. The study by [75] included adolescents (age 12 to 15 years), and reported a correlation coefficient between water fluoride and dental fluorosis severity of 0.97 (p-value <0.05). In the bivariate analysis, the study reported 1.76 (1.31, 2.38) times greater odds (95% CI) of dental fluorosis (any fluorosis, measured using the Modified Dean's Index) among participants exposed to water fluoride levels >1.2 ppm compared to ≤1.2 ppm.

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[86] included adolescents (age 12 to 17 years), and demonstrated a positive correlation (rho = 0.57) between the Community Fluorosis index (CFI) and levels of fluoride in drinking water. The study by [91] included children (age 9 years), and reported the frequency of participants with genuine fluorosis (excludes fluorosis-resembling defects) as 42 (47.7%), 39 (20.6%), and 3 (3.3%) in areas with high, optimal, and low levels of fluoride, respectively. Compared to areas with high levels of fluoride, the odds of genuine dental fluorosis were 70.8% (OR= 0.29, 95% CI: 0.17, 0.51) and 96.3% (OR= 0.04, 95% CI: 0.01, 0.13) less in areas with optimal and low levels of fluoride, respectively. In general, studies identified by the current literature search reported a wide range of fluoride concentrations ranging from 0.06 ppm in Brazil [44] to >4 ppm in Iran [91].

Further to a study conducted in 2022 in Canada [105] where the reported fluoride levels in tap water was 0.1 – 1.0 ppm, other examples of fluoride concentrations relevant to the North American context were reported from Ireland (tap water, 0.6 – 1.0 ppm) [29], China (tap water, 0.89 – 0.91 ppm) [92], Mexico (tap water, 1.22 ±1.09 ppm) [67], and India (tap water, 0.67-0.83 [404], 1.1–2.92 [10] [17] and 1.27 ±0.46 ppm [75]). Only 2 studies [29, 51] reported non-significant (possible) association between high drinking water fluoride (>6 ppm) and dental fluorosis.

Although no meta-analysis was conducted for the current review, an earlier review [106] included a dose-response meta-analysis of 40 studies at high risk of bias (published up to that time). The results suggested that at 0.4 ppm fluoride, 10% of a population (95% CI: 6%-15%) would be expected to have dental fluorosis of aesthetic concern (defined as ≥3 TFI, ≥2 TSIF, or mild or worse DFI) [odds ratio= 2.90 (95% CI 2.05 to 4.10) for each 1 mg/L increase of fluoride exposure].

Current review evidence synthesis: Several newer studies have been published since the CADTH 2019 review, adding to the large body of literature on fluoride and dental fluorosis effects. Evidence in these new studies is consistent with previously published work for the prevalence of dental fluorosis in populations with varying levels of fluoride in drinking water.

Fluorosis, skeletal

Earlier evidence on the association of fluoride with skeletal fluorosis was reported by NHMRC 2016 [99, 100] (one systematic review at 3.8 to 8 ppm and two studies of low quality at <4, 4 to 6, and >6 ppm for one study, and 1.51 to 3.71 ppm for the other study) and CADTH 2019 [2] (two studies of low quality at North American CWF levels). Evidence was collectively reported by CADTH 2019 as 638

insufficient to conclude an association. The current literature review search identified 3 cross-sectional studies with high/acceptable quality that were conducted in China [64], Ethiopia [22], and India [30] on individuals aged 10 years or older. Whereas only 1 study [22] reported a positive association between fluoride exposure and skeletal fluorosis, the 2 other studies of acceptable quality reported a possible impact [30, 64]. Reported ground water fluoride levels included a mean (SD) of 6.8 ppm (±4.3) in one study and a wide range of ≤1 – >4.0 in another study. No water fluoride levels could be extracted, or extrapolated from the third study[64].

Current review evidence synthesis: Based on the available literature to date, there is limited evidence for an association of skeletal fluorosis with fluoride exposures relevant to North American drinking water.

Genotoxicity

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and genotoxicity. The current literature search identified 2 cross-sectional studies that were conducted in China with high [31] or acceptable quality [70]. Whereas the first study [31] suggested a possible association of fluoride exposure (1.1 – 4.1 ppm) with disrupting DNA methylation, the second study [70] concluded a positive association of low-moderate water fluoride exposure (0.60 ppm) and disrupting circulating mitochondrial DNA (mtDNA) levels.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of genotoxicity and fluoride exposures relevant to current North American drinking water levels.

Growth and development

BMI

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and BMI. The current literature search identified an ecological study [90] with acceptable quality that was conducted on Indian children and adolescents (6-18 years old), which reported a positive and non-significant correlation between water fluoride levels (range: 0.25-9.4 ppm; average: 2.1 ppm) and BMI.

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Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of BMI and fluoride exposures relevant to current North American drinking water levels.

Childhood obesity

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure with childhood obesity. The current literature search identified a single cross-sectional study [61] with high quality that was conducted on Chinese children and adolescents aged 7–13 years old from ground water-supplied areas. The study reported an association of low-to-moderate exposure to fluoride (0.83 ppm) with overweight status and obesity in children.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of childhood obesity and fluoride exposures relevant to current North American drinking water levels.

Newborn's height and weight

A single study of low quality was reported by NHMRC 2016 [99, 100], which reported that mothers exposed to drill water with a fluoride level of 4.7 ppm were more likely to have low birth weight newborns. Another study with low quality, as reported by CADTH 2019 [2], showed a positive correlation between drinking water fluoride and infant height and weight. The current review did not identify any additional studies for this endpoint.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and newborns' weight or newborns' height.

Kidney diseases

Kidney, dysfunction

There were no earlier studies identified in NHMRC 2016 [99, 100] that reported on the association of fluoride and kidney dysfunction. In 2019, the review by CADTH 2019 [2] identified a single study with low quality and concluded that there was insufficient evidence on the association between CWF and kidney dysfunction.

The current literature search identified 4 studies with high quality and 2 studies with acceptable quality, which examined the association of fluoride exposure with kidney dysfunction. Four out of these 6 studies reported results consistent with a possible association [49, 57, 62, 73]. The first study [62] was cross-sectional in design that was conducted on US adolescents (12-19) as part of the NHANES survey, which suggested a possible association with complex changes in kidney functions. A second cross-sectional study [73] was conducted on Mexican adults (18-77 years old) who were exposed to high drinking water fluoride levels. The study reported a possible fluoride-associated kidney tubular dysfunction, with a likely impact on future development of chronic kidney dysfunction. A third cross-sectional study with acceptable quality [49] was conducted on men diagnosed with CKDu, and concluded a possible association with serum fluoride. A fourth Sri Lanka-based study of case-control design with acceptable quality [57] was conducted on 19-76 years old, non-dialysis, biopsy-proven CKDu adult cases. Study suggested a possible association between fluoride exposure and CKDu. These 4 studies reported kidney dysfunction at water fluoride concentrations of 0.48 ppm [62], 1.33 ppm [57], 1.5 ppm [73] and 0.68 ppm (±0.48)[49].

One cross-sectional study with high quality was conducted on 5-12 years old Mexican school children [58], and reported an inconclusive association with kidney disease of unknown origin (CKDU) at a fluoride concentration of 0.3 ppm. Another cross-sectional study conducted on Mexican children (5-12 years old) reported no association between kidney injury biomarkers and fluoride [87] at a concentration of 2.47 ppm.

Current review evidence synthesis: Based on the available literature to date, there is limited evidence for an association of kidney dysfunction (mainly CKDu) and fluoride exposures relevant to current North American drinking water levels.

Kidney, stones

The review by CADTH 2019 [2] concluded there was limited evidence for an inverse association between fluoride exposure and development of kidney stones based on a single study with

acceptable quality. There were no studies identified in NHMRC 2016 [99, 100] or Current literature search that reported on the association of fluoride exposure with kidney stones.

*Current review evidence synthesis: I*n the absence of new studies, the CADTH summary of evidence remains unchanged: Limited evidence for an inverse association between water fluoridation at current North American levels and the incidence of kidney stones.

Kidney, ultrastructural

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure with ultrastructural changes in the kidney. The current literature search identified a single study of acceptable quality, which was conducted in India on children (4-12 years old) with nephrotic syndrome minimal change disease (NS-MCD). Although the study was case-control in design, only cross-sectional analysis results relevant to the current review were included. The study reported a positive association between fluoride exposure and ultrastructural changes and apoptosis in human renal tubules [80]. However, no water fluoride levels were extracted or extrapolated from this identified study.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of ultrastructural changes in the kidney and fluoride exposure.

Liver dysfunction

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure with liver dysfunction. The current literature search identified two studies, which examined the association of fluoride exposure with liver dysfunction. The first [62] was cross-sectional in design, that examined data on US adolescents (12-19) as part of the NHANES survey, and suggested a possible association between water fluoride (0.48 ppm) and complex changes in liver functions in adolescents. Another case-control study with acceptable quality [84] was conducted on patients with dental and skeletal fluorosis in India, which reported that prolonged water fluoride (>1.5 ppm) could overwhelm the regenerative capacity of liver tissues leading to liver damage.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of liver dysfunction and fluoride exposures relevant to current North American drinking water levels.

Neurologic

Neurologic, Headache

The NHMRC 2016 [99, 100] examined two studies with low quality, which did not provide a clear conclusion on the association between fluoride and headache symptoms. No studies were identified in CADTH 2019a [3]. Current literature search identified 1 study [22] that reported a possible association between headache and paresthesia at ground water fluoride level of 6.8 ±4.3 ppm.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of headache and paresthesia and fluoride exposures relevant to current North American drinking water levels.

Neurologic, Sleep-related Outcomes

The NHMRC 2016 [99, 100] examined two studies with low quality, which did not provide a clear conclusion on the association between fluoride exposure and insomnia. CADTH 2019a [3] literature search did not identify any new studies. The current literature search identified a single cross-sectional study with high quality [63] that was conducted on US adolescents (16-19) as part of the NHANES survey (2015–2016). This study reported positive and significant associations between water fluoride levels (0.39 ppm) and sleep apnea, bedtime and wake time; non-significant positive associations with the recommended sleep duration and daytime sleepiness; possible and significant inverse association and snoring among males; and no association with trouble sleeping.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of sleep-related outcomes and fluoride exposures relevant to current North American drinking water levels.

Reproduction

Reproduction, abortion and fertility

Two studies of low quality were identified earlier by CADTH 2019 [2], which did not provide a clear conclusion between water fluoride level and rates of abortion. There were no studies identified in NHMRC 2016 [99, 100] or Current literature search that reported on the association of fluoride exposure with abortion.

Current review evidence synthesis: In the absence of new studies, the CADTH summary of evidence remains unchanged: Insufficient evidence for an association between water fluoridation at current North American levels and reproduction in women.

Reproduction, preterm births

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and preterm births. The current literature search identified a single cross-sectional study of high quality, that was conducted on US women with a live birth (2009-2016) who responded to the PRAMS survey (Pregnancy Risk Assessment Monitoring System) [68]. The study reported that women who had dental cleaning during pregnancy and lived in a community with water fluoridation had lower prevalence of preterm births. However, no water fluoride levels could be extracted, or extrapolated from this identified study.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of preterm births and fluoride exposure.

Reproduction, sex hormone disruption

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and disruption of male sex hormones. The current literature search identified 2 cross-sectional studies of high quality that examined US children and adolescents 6–19 years old (NHANES survey) [41], and male farmers from Henan Province in China [55]. Results from the first study [41] indicated a gender- and age-specific inverse associations of fluoride in plasma and water with sex steroid hormones of total testosterone, estradiol and SHBG in U.S. children and adolescents, with a mean water fluoride level of 0.36 ppm (0.30 – 0.42). The

second study [55] reported a significant inverse association between water fluoride level and serum sex hormone binding globulin (SGBH) levels but not with androgen binding protein (ABP) levels. The average fluoride concentration in villages in the high exposure group (HEG) was 2.44 ± 1.88 mg/L, and in the control, low exposure villages (LEG) was 0.37 ± 0.15 mg/L. The current review also identified a relevant abstract [4] that reported a possible association with altering the hypothalamic testicular axis hormones in human males residing in high fluoride regions. There were insufficient details on the study in the published abstract.

Current review evidence synthesis: Based on the available literature to date, there is limited evidence for an association of levels of sex hormones and fluoride exposures relevant to current North American drinking water levels.

Thyroid dysfunction

Evidence on the association of fluoride with thyroid gland dysfunction was reported on by NHMRC 2016 [99, 100] (3 studies of low quality) and CADTH 2019 [2] (1 study of acceptable and three studies of low quality), which concluded mixed findings, flagging insufficient evidence for this association.

The current review identified seven relevant studies, which were all of cross-sectional design, and were conducted on children and adolescents. Three studies were conducted in India [66, 74, 81], 3 in China [25, 42, 54], and 1 in Canada [76]. Four studies of high [25, 54] or acceptable quality [74, 81] reported a positive association with thyroid dysfunction, 1 study of high quality reported a possible association [76], and 1 study of acceptable quality that reported a non-significant association [42] with thyroid dysfunction. These studies identified disruption of thyroid hormones at water fluoride concentrations of 0.22 ppm [76], <1ppm [81], 1.39 ppm [54], and 2.88 ppm [74]. A seventh study of acceptable quality reported no association between disruption of thyroid functions and drinking water fluoride levels (0.01-2.0 ppm) [66].

Current review evidence synthesis: Based on the available literature to date, there is limited evidence to evaluate the association of thyroid hormone disruption and fluoride exposures relevant to current North American drinking water levels.

Other outcomes

Arsenic methylation

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and arsenic methylation. The current literature search identified a single cross-sectional study of high quality that was conducted on Mexican adults. The study reported a positive association between water fluoride exposure (1.6 ppm) and increasing arsenic (As) toxicity in adults, which has been linked to adverse health outcomes such as cancer, cardiovascular diseases, diabetes and cardiometabolic risk [59].

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of arsenic methylation and fluoride exposures relevant to current North American drinking water levels.

General health

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and general health. The current literature search identified a large cross-sectional study [89] with acceptable quality that was conducted using data on >500,000 US adolescents and adults from the National Health and Nutrition Examination Survey III (NHANES III). The study reported a lack of evidence for an effect of water fluoridation (0.3-3 ppm) on general health.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of general health and fluoride exposures relevant to current North American drinking water levels.

Other non-skeletal manifestations of fluoride toxicity

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure with non-skeletal manifestations of fluoride toxicity (referred to as non-skeletal fluorosis by some authors). The current literature search identified 2 cross-sectional studies with acceptable quality that were conducted in Ethiopia [22] and India [82]. The first one [22] reported a possible association between fluoride exposure from ground water and multiple

manifestations including loss of appetite, constipation, and fatigue. Participants were 10–70 years old from rural areas who were exposed to groundwater fluoride levels with a mean concentration of 6.8 ±4.3 mg/L (range: 0.3–15.5 mg/L). The second study [82] compared individuals living in areas with high-fluoride exposure to those in normal fluoride exposure areas. The study reported that non-skeletal manifestations of fluoride toxicity (dyspepsia, fatigue and muscle weakness) may be due to fluoride exposure through water (>1.5 ppm) or other sources like food.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of the listed non-skeletal manifestations of fluoride toxicity and fluoride exposure.

Suicide

There were no earlier studies identified in NHMRC 2016 [99, 100] or CADTH 2019 [2] that reported on the association of fluoride exposure and suicide. The current literature search identified a single relevant abstract [5], which reported a possible association between fluoride exposure and reduction in suicide rates. However, no water fluoride levels were extracted or extrapolated from this identified abstract.

Current review evidence synthesis: Based on the available literature to date, there is insufficient evidence to evaluate an association of suicide and fluoride exposure.

2.5. Summary of evolving human evidence on all endpoints

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
All-cause, mortality	1 study (N= 208,570,962, acceptable) *A small reduction in incidence rate of all-cause mortality in CWF areas. Difference in rate was: -1.3% (95% CI: -2.4%, 0.1%).*	No studies	Insufficient evidence for an association at current North American CWF levels.	No new studies	Insufficient evidence for an association at current North American CWF[xxxv] levels.
Bone, cancer	2 SR[xxxvi] (2 NR[xxxvii]); 6 studies (3 acceptable, 3 low) • 1 SR (8 studies; N=NR) *No clear association between water fluoridation and the incidence rate of osteosarcoma*	2 studies (2 acceptable; N=1,663 and N=710,260,000 person-years) *Two studies with partial applicability to the North American context showed no significant*	Consistent evidence for no association at current North American CWF levels.	3 studies (1 high, 2 acceptable) • 1 study (N=645, acceptable). *No association between CWF and bone cancer* [46] • 1 study (N=4,406,021, high). *No association between CWF and bone cancer. Risk was a little high due to smaller*	Sufficient evidence for no association at fluoride exposures relevant to current North

[xxxv] CWF: Community water fluoridation

[xxxvi] SR: Systematic review

[xxxvii] NR: Not reported

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Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	• 1 SR (1 study; N= 318) *Higher exposure to fluoridated water was associated with a higher risk of developing osteosarcoma in males, but not in females* • 5 studies (N > 253,768,952, partial applicability to the North American context) *No significant difference in the incidence rate of osteosarcoma in children and adults between high and low exposure to water fluoridation* • 1 study (N=20)	*difference in incidence rate of osteosarcoma in children and adults between high and low fluoride level areas.*		*sample size compared to the other examined bone diseases [48].* • 1 study (N=24,661, acceptable). *No association with secondary bone cancer [56].*	American DWL[xxxviii].

[xxxviii] DWL: Drinking water levels

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	A conclusion could not be drawn from a low-quality study from India with high risk of bias				
Bone, density and quality	1 SR (NR); 1 study (low) • 1 SR (27 studies; N=NR) *Addition of fluoride to drinking water at the level of 1 ppm did not associate with a decrease in bone mineral density compared with non-fluoridated water.* • 1 study (low, N= 675) *Prevalence of osteoporosis was not significantly different between groups. (Limited)*	No studies	Insufficient evidence for an association at current North American CWF levels.	5 studies (4 high and 1 acceptable) • 1 study (N=4,306, high) *Positive association with increasing bone mass density and skeletal fragility in older women* [28] • 1 study (N=4,406,021, high) *No association between CWF and osteoporosis.* [48]. • 1 study (N=722, high) *Positive association with decreasing BMD in women* [52] • 1 study (N=341, high) *Negative association with bone quality* [45]. • 1 study (N=380, acceptable)	Inconsistent evidence for an association at current North American CWF levels.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				No association with bone quality [79].	
Bone, hip fracture	2 SRs (2 NR); 2 studies (acceptable) • 2 SRs (19 studies; N=NR) *No clear association between water fluoridation and hip fracture incidence in adults.* • 2 studies (acceptable; N=313,329,725) *No increased risk of hip fracture from water fluoridation exposure.*	1 study (acceptable; N=477,610,000 person-years) *A weak association between water fluoridation and hip fracture observed in females, but not in males.*	Consistent evidence for no association with CWF levels.	1 study (high) • 1 study (N=4,406,021, high). *No association between CWF and risk of hip fractures in older women* [48].	Sufficient evidence for no association at fluoride exposures relevant to current North American DWL.
Bone, musculoskeletal pain	2 studies (2 low; N=3,266) *Increased risk of lower back pain and joint pain associated with higher fluoride levels. The results were from studies*	No studies	Insufficient evidence for an association at current North American CWF levels.	No new studies	Insufficient evidence for an association at current North American CWF levels.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	of low quality and from countries where socio-economic parameters differed than those in Canada.				
Cancer, total, *incidence and mortality*	SRs (2 NR); 3 studies (acceptable) • 2 SR (13 studies; N=NR) *No clear association between water fluoridation and overall cancer incidence* • 1 study (N=208,770,962) *No significant difference in the incidence of all cancer between CWF and non-CWF* • 1 study (N=555,127,448) *Significantly lower incidence rate of*	1 study (acceptable; N=827,660,000 person-years) *Incidence of bladder cancer was lower in fluoridation areas. Odds ratio was 0.94 (95% CI, 0.90 to 0.98).*	Consistent evidence for no association at current North American CWF levels.	No new studies	Sufficient evidence for no association at current North American CWF levels.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	invasive bladder cancer in CWF. Difference in rate= –8.0% (95% CI: –9.9%, –6.0%) • 1 study (N=NR) *An inverse correlation between the percentage of the population receiving fluoridated water and incidence of eye cancer (r= –0.45; P=0.002).*				
Cognitive, ADHD	No studies	No studies	N/A	2 studies (2 high) • 1 study (cycle 2: N=2,520; cycle 3: N=2,667, high). *Positive association with ADHD among North American youth, particularly among adolescents* [65]. • 1 study (N=213, high).	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				Positive association with inattention, but not hyperactivity or impulse control (ADHD) in children due to prenatal exposure to fluoride [71].	
Cognitive, dementia	No studies	No studies	N/A	• 1 study (N=6,980, high). *Positive association with dementia risk* [50].	Insufficient evidence for an association
Cognitive, Down syndrome	2 SRs (2 NR); 1 study (acceptable) • 2 SRs (N= NR) *No clear association between water fluoridation and Down syndrome.* • 1 study (N=2,272,300) *No significant difference in the incidence rate of Down syndrome between CWF and non-CWF.*	1 study (acceptable; N=2,020,259) *No significant difference in the incidence rate of Down syndrome by fluoridation status*.	Limited evidence for no association at current North American CWF levels.	No new studies	Limited evidence for an association at fluoride exposures relevant to current North American DWL.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
Cognitive, reduction in IQ score	1 SR (NR); 11 studies (1 high, 2 acceptable, 8 low) • 1 SR (2 studies; N=NR) *No evidence of sufficient quality to make any conclusions for a relationship between water fluoridation and IQ in children or cognitive impairment in adults.* • 1 study (N=992 children and 942 adults; high quality and partial applicability to the North American context) *No difference in mean IQ scores of children and adults between fluoridated water (0.7 ppm-1.0 ppm) and naturally occurring water fluoride (0.0 ppm-0.3 ppm).*	6 studies (1 acceptable, 5 low) • 1 study (N=NR, acceptable) *No effect of water fluoride on cognitive ability, non-cognitive ability, and math test in participants aged ≥ 16 years in Sweden.* • 1 study (N=2,220, low) *No clear association between fluoride exposure and reported learning disability among North American children aged 3 to 12 years.*	Limited evidence for no association at current North American CWF levels.	21 studies (12 high, 9 acceptable) • 1 study (N=386, high) *Positive association of prenatal exposure to fluoride with sustained impacts on IQ* [11]. • 1 study (N=316, high) *Results in boys suggest improved scores in cognitive domains with maternal urinary concentrations* [13]. • 1 study (N=148, high) *Positive association between high fluoride exposure and lower IQ levels* [18]. • 1 study (N=596, high) *Positive association of IQ with prenatal and postnatal fluoride exposure, which may be modified by sex (further evidence needed)* [26].	Sufficient evidence for a positive association with lowering IQ scores in children at fluoride exposures relevant to current North American DWL.

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Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	• 10 studies (N= 1,445) *Mixed findings on the relationship between water fluoridation and IQ or cognitive function from low quality studies with limited applicability to the North American context.*	• 4 studies (N=1,341, low) *Mixed findings from studies of low quality and with limited applicability to the North American context.*		• 1 study (N=709, high) *Positive association between low-to-moderate fluoride exposure with alteration of IQ* [37]. • 1 study (N=952, high) *Positive association between intelligence and fluoride, and possibly with the interaction of fluoride with mitochondrial function-related SNP-set, genes and pathways* [39]. • 1 study (N=567, high) *Positive association of exposure to drinking water fluoride and IQ in children. Dopamine-related genes polymorphism may modify the effects of such exposure* [40]. • 1 study (N=571, high). *Positive association with alterations in childhood thyroid*	

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				function that may modify the association between fluoride and intelligence (IQ scores) [54]*.* • 1 study (N=398, high). *Positive association with diminished non-verbal intellectual abilities (performance IQ)* [53]*.* • 1 study (N=2,886, high). *Negative association with IQ scores* [83]*.* • 1 study (N=323, high). *Negative association with IQ scores in children carrying the dopamine receptor-2 (DRD2) Taq 1A- TT genotype. No association with the other DRD2 Taq 1A genotypes* [72]*.* • 1 study (N=299, high). *Positive association of prenatal exposure with lower GCI (IQ) scores in children at*	

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				approximately 4 y old, and with lower Full-Scale IQ scores at 6–12 y old [85].	
				• 1 study (n=90, acceptable) *Positive association between excess drinking water fluoride exposure and IQ reduction* [14].	
				• 1 study (n=100, acceptable) *Positive association of intelligence of children with prevalence of fluorosis, with the intelligence level of those in high-exposure areas being lower than those in low-exposure areas* [38].	
				• 1 study (n=683, acceptable) *Positive association of IQ reduction with fluoride exposure, as well as with fluoride's interaction with MTHFD1 polymorphisms* [9].	

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				• 1 study (N >500.000, acceptable). *No evidence of an effect of water fluoridation on retardation in children* [89]. • 1 study (N=149, acceptable). *Negative correlation with IQ* [90]. • 1 study (N=498, acceptable) *Some non-significant frequency differences between urinary fluoride levels and reducing IQ scores* [42] • 1 study (N=775, acceptable). *Possible inverse association with schooling performance (IQ)* [78]. • 1 study (N=120, acceptable) *No significant difference was present between the IQ distribution in the high and low fluoride areas* [8].	

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				• 1 study (N=498, acceptable) *No association between fluoride and IQ scores* [67]	
Cognitive, trouble working	No studies	No studies	N/A	• 1 study (N >500.000, acceptable). *No evidence of an effect of water fluoridation on trouble working for children or adults* [89].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
CVD, atherosclerosis	1 study (N= 500, low) *Significantly higher risk of carotid artery atherosclerosis in adults in areas with high fluoride levels (>1.2 ppm).*	No studies	Insufficient evidence for an association at current North American CWF levels.	3 studies (1 high, 2 acceptable) • 1 study (N=31, acceptable) *Children in the fluorosis area had higher blood TBARS levels, while the acyl hydroperoxide levels were non-significantly increased in comparison with healthy children living in the non-fluorosis area* [36].	Limited evidence for an association at fluoride exposures relevant to current North American DWL.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				• 1 study (N= 374, high). *Significant positive association of urinary fluoride with cardiovascular diseases' markers VCAM-1, ICAM-1 and cIMT, significant negative association with sCys-C, and no significant association with ET-1* [58]*.* • 1 study (N= 508, acceptable). *Positive correlation with erythrocyte TBARS (p <0.01), plasma TBARS (p <0.05), cholesterol (p <0.01) and LDL (p <0.01). Significant inverse association with PON1, ARE, and lactonase. No significant association with TGL and VLDL. No observed correlation with serum HDL; however, serum fluoride modulates the activities of PON1, ARE and lactonase,*	

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				which might be useful for predicting the risk of atherosclerosis in fluorosis patients [84].	
CVD, hypertension	3 studies (low; N>160,637) *Mixed findings from studies of low quality and derived from countries where fluoride levels were many times higher than the current North American levels*	2 studies (2 low; N=3,224) *Mixed findings from studies of low quality and from countries where fluoride levels were many folds higher than the current North American levels (2 studies*	Insufficient evidence for an association at current North American CWF levels.	No new studies	Insufficient evidence for an association at current North American CWF levels.
CVD, myocardial infarction	No studies	1 study (low; N=474,217) *No significant difference in the risk of myocardial infarction and water*	Insufficient evidence for an association at current North American CWF levels.	• 1 study (N=31, acceptable) *Children in the fluorosis area had higher blood TBARS levels, while the acyl hydroperoxide levels were non-significantly increased in comparison with healthy*	Insufficient evidence for an association at current North American CWF levels.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
		fluoride levels in Sweden.		*children living in the non-fluorosis area* [36].	
Diabetes Mellitus	No studies	2 studies (2 low) • 1 study (N=NR) *No convincing evidence for an association between water fluoride levels and incidence of type 1 diabetes in Canada* • 1 study (N=NR) *A positive relationship between added fluoride in drinking water, even at optimum level, and the incidence and prevalence of diabetes in the US.*	Insufficient evidence for an association at current North American CWF levels.	• 1 study (N=92, high) *The increase in serum Fluoride increases diabetes mellitus and diabetic nephropathy* [47]	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.

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Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
Eye, diseases	No studies	No studies	N/A	• 1 study (N= 1, 813, high). *Possible (significant) positive association of water fluoride levels with pterygium and arteriosclerotic retinopathy, and significant inverse association with cataract. Non-significant associations with primary angle closure glaucoma, diabetic retinopathy, age-related macular degeneration, and strabismus* [69].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
Eye, refractive errors	No studies	1 study (low; N=1,415) *No difference in prevalence of refractive errors (myopia, hyperopia, astigmatism) between high and low water fluoride levels.*	Insufficient evidence for an association at current North American CWF levels.	No new studies	Insufficient evidence for an association at current North American CWF levels.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
Fluorosis, dental	3 SRs (2 NR, 1 high) • 1 SR (88 studies; N= NR) *Prevalence increased with water fluoride levels. Prevalence of dental fluorosis of any level of severity at 1 ppm was 48% (95% CI, 40 to 75), of which 12.5% (95% CI, 7.0 to 21.5) had fluorosis of aesthetic concern.* • 1 SR (10 studies; N= NR) *A fourfold higher risk in the development of overall dental fluorosis and fluorosis of aesthetic concern in optimal water fluoridation compared with non-CWF. The absolute increase in prevalence*	21 studies (1 acceptable, 20 low; N= 35,374) *In all studies, dental fluorosis prevalence and its severity increased with increased water fluoride levels (21 studies;). The majority of evidence (17 out of 21 studies) derived from countries where water fluoride levels were many folds higher than the current North American levels.*	Consistent evidence for an association at current North American CWF levels.	33 studies (15 high, 18 acceptable) • Thirty-two studies (3 studies (15 high quality [15, 18, 19, 23, 24, 29, 32, 33, 35, 37, 70, 75, 86, 91, 105] and 17 acceptable [6, 7, 10, 12, 17, 20, 21, 27, 34, 38, 43, 44, 60, 67, 77, 88, 92] *These studies reported a positive association with dental fluorosis at a wide range of fluoride concentration in drinking water (both tap and ground).* • Only 1 study [51] (acceptable, N= 1,397) *Study reported no significant association between high drinking water fluoride and dental fluorosis.*	Sufficient evidence for a positive association at fluoride exposures relevant to current North American DWL.

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Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	was 26% and 5%, respectively. • 1 SR (90 studies; N= 59,630) *Prevalence of any level at 0.7 ppm was 40%, of which 12% had fluorosis of aesthetic concern*				
Fluorosis, skeletal	1 SR (NR); 2 studies (2 low) • 1 SR (1 study; N=NR) *Skeletal fluorosis found only in areas of high fluoride levels (3.8 ppm to 8.0 ppm).* • 2 studies (2 low, N=2,816) *No clear relationship between water fluoride level and prevalence of skeletal fluorosis (<4, 4 to 6, and >6 ppm for one*	2 studies (2 low; N=1,595) *Mixed findings from studies of low quality and from countries where fluoride levels were many folds higher that current North American levels.*	Insufficient evidence for an association at current North American CWF levels.	3 studies (1 high, 2 acceptable) • 1 study (N=316, high) *Positive association between fluoride and skeletal fluorosis* [22]. • 1 study (N=3,268, acceptable) *Possible association between fluoride and skeletal fluorosis* [30] • 1 study (N=302, acceptable). *Possible impact on some of the genetic biomarkers of skeletal fluorosis* [64].	Limited evidence for an association with fluoride exposure relevant to North American DWL.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
	study, and 1.51 to 3.71 ppm for the other study).				
Genotoxicity	No studies	No studies	N/A	2 studies (1 high, 1 acceptable) • 1 study (N=281, acceptable) *Possible association of fluoride exposure with disrupting DNA methylation* [31]. • 1 study (N=616, high) *Positive association of low-moderate water fluoride exposure and disrupting circulating mitochondrial DNA (mtDNA) levels* [70].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
Growth & development, BMI	No studies	No studies	N/A	• 1 study (N=149, acceptable). *Positive, non-significant correlation with BMI* [90].	Insufficient evidence for an association at fluoride exposures relevant to

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
					current North American DWL.
Growth & development, childhood obesity	No studies	No studies	N/A	• 1 study (N=2,340, high). *Low-to-moderate fluoride exposure is associated with overweight and obesity in children. Gender and paternal education level may modify the relationship* [61].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
Growth & development, Newborn's height & weight	1 study (low; N=324) *Mothers exposed to drill water with a fluoride level of 4.7 ppm had higher risk to have low birth weight newborns.*	1 study (low; N= 492) *A positive correlation between babies' height (r = 0.69; P < 0.001) or babies' weight (r = 0.44; P < 0.001) and drinking water fluoride.*	Insufficient evidence for an association at current North American CWF levels.	No new studies.	Insufficient evidence for an association at current North American CWF levels.
Kidney, dysfunction	No studies	1 study (low; N= 824) *No conclusion could be drawn due to*	Insufficient evidence for an association at current North	6 studies (4 high, 2 acceptable) • 1 study (N=311, acceptable)	Limited evidence for an association at fluoride

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
		significant methodological limitations and lack of statistical analysis.	American CWF levels.	*Possible association with chronic kidney disease of unknown origin (CKDU)* [49] • 1 study (N=4,470, high). *Possible association with kidney functions (lower estimated glomerular filtration rate and blood urea nitrogen concentration, and slightly elevated serum uric acid concentration) in adolescents* [62]. • 1 study (N= 239, high). *Possible association with kidney tubular dysfunction* [73]. • 1 study (N=193, acceptable). *Possible association with chronic kidney disease of unknown origin (CKDU)* [57]. • 1 study (N= 374, high). *Inconclusive association of fluoride exposure with kidney*	exposures relevant to current North American DWL.

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Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				injury (increased eGFR, decreased uCys-C, and no significant association with KIM-1) [58]. • 1 study (N= 83, high). *No association was found between kidney injury biomarkers and fluoride* [87].	
Kidney, stones	No studies	1 study (acceptable; N=47,610,000 person-years) *Lower incidence of emergency admissions for kidney stones in CWF areas in England. Incidence rate ratio was 0.90 (95% CI, 0.82 to 0.98).*	Limited evidence for an inverse association at current North American CWF levels.	No new studies	Limited evidence for an inverse association at current North American CWF levels.
Kidney, ultrastructural	No studies	No studies	N/A	• 1 study (N=156, acceptable).	Insufficient evidence for an association with

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				Positive association with ultrastructural changes and apoptosis in human renal tubules [80].	fluoride exposure.
Liver dysfunction	No studies	No studies	N/A	2 studies (1 high, 1 acceptable) • 1 study (N=4,470, high). *Possible association between fluoride exposure and complex changes in liver functions* [62]. • 1 study (N= 508, acceptable). *Increased LDH5 isoenzyme (liver synthesized) activity is an indication of possible liver damage in fluorosis patients. Therefore, prolonged fluoride ingestion overwhelmed the regenerative capacity of liver tissues. Serum fluoride modulates the activities of PON1, ARE and lactonase, which might be useful for*	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				predicting the risk of liver diseases in fluorosis patients [84].	
Neurologic, Headache	2 studies (2 low; N=5,342) *No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis.*	No studies	Insufficient evidence for an association at current North American CWF levels.	• 1 study (N=316, acceptable) *Possible association between fluoride and headache and paresthesia* [22].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
Neurologic, Sleep-related Outcomes	2 studies (2 low; N=5,342) *No conclusion could be drawn for the association of fluoride exposure and insomnia due to significant methodological limitations and lack of statistical analysis.*	No studies	Insufficient evidence for an association at current North American CWF levels.	• 1 study (N= 419, high). *Fluoride exposure may contribute to changes in sleep cycle regulation and sleep behaviors among older adolescents in the US. Positive and significant association between water fluoride levels and sleep apnea, bed time and wake time. Non-significant positive*	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				association with recommended sleep duration and daytime sleepiness. Possible (significant) inverse association between water fluoride levels and snoring among males. No association with trouble sleeping [63]*.*	
Reproduction, abortion and fertility	No studies	2 studies (2 low; N=5,993) *No clear relationship between water fluoride level and rates of abortion and fertility due to lack of controlling for confounders, from studies of low quality and of limited applicability to the North American context.*	Insufficient evidence for an association at current North American CWF levels.	No new studies	Insufficient evidence for an association at current North American CWF levels.

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
Reproduction, preterm births	No studies	No studies	N/A	• 1 study (N=9,234, high). *Women who had dental cleaning during pregnancy and lived in a community with water fluoridation had lower prevalence of preterm birth (significant). Water fluoridation alone was inversely associated (non-significant) with prevalence of preterm births* [68].	Insufficient evidence for an association with fluoride exposure.
Reproduction, sex hormone disruptions	No studies	No studies	N/A	2 studies (2 high), 1 abstract (N/A) • 1 study (N=3,392, high) *Significant inverse associations of fluoride in plasma and water with sex steroid hormones of total testosterone, estradiol and SHBG in U.S. children and adolescents* [41]. • 1 study (N= 348, high).	Limited evidence for an association at fluoride exposures relevant to current North American DWL.

Trial Ex. 131.674

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
				Significant inverse association between urinary fluoride levels and serum sex hormone binding globulin levels: SHBG (significant) and ABP (non-significant) [55]. • 1 abstract (N= 100, N/A). *Possible association with altering the hypothalamic testicular axis hormones in human males residing in high fluoride regions (insufficient study information)* [4].	
Thyroid function	3 studies (3 low) • 3 studies (N=789) *Mixed findings from studies of low quality and with limited applicability the North American context.*	4 studies (1 acceptable, 3 low) • 1 study (N=5,201) *No association between fluoride exposure and impaired thyroid functioning in the*	Insufficient evidence for an association at current North American CWF levels.	7 studies (3 high, 4 acceptable) • 1 study (N=446, high) *Positive association with thyroid dysfunction (TSH, Tvol)* [25]. • 1 study (N=498, acceptable). *Non-significant frequency differences between urinary fluoride levels and TSH* [42]	Limited evidence for an association at fluoride exposures relevant to current North American DWL.

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Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
		North American population. • 1 study (N=7,935 GP practices) *Significantly higher odds of GP practice recording high levels of hypothyroidism in areas with fluoridation compared with areas without fluoridation in the US* • 2 studies (N=1,037) *No clear relationship between water fluoride and thyroid function from studies of low quality and with limited applicability to the*		• 1 study (N=6,914,124, high). *Possible association with thyroid hypofunction* [76]. • 1 study (N=571, high). *Positive association with alterations in childhood thyroid function that may modify the association between fluoride and intelligence (IQ scores)* [54]. • 1 study (N=400, acceptable). *Positive association with alteration in thyroid hormones activity* [74]. • 1 study (N=100, acceptable). *Positive association with increased thyroid hormone levels* [81]. • 1 study (N=293, acceptable). *No association with thyroid functions in children with*	

Trial Ex. 131.676

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
		North American context.		*normal nutritional status and optimal iodine intake* [66].	
Other outcomes, arsenic methylation	No studies	No studies	N/A	• 1 study (N=236, high). *Positive association with increasing arsenic (As) toxicity in adults, which has been linked to adverse health effects such as cancer, cardiovascular diseases, diabetes and cardiometabolic risk* [59].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
Other outcomes, general health	No studies	No studies	N/A	• 1 study (N >500.000, acceptable). *No evidence of an effect of water fluoridation on general health* [89].	Insufficient evidence for an association at fluoride exposures relevant to current North American DWL.
Other outcomes, other non-skeletal	2 studies (2 low; N=5,342)	No studies	Insufficient evidence for an	2 studies (acceptable) • 1 study (N=316, acceptable)	Insufficient evidence for an

Trial Ex. 131.677

Outcome	NHMRC 2016	CADTH 2019 new evidence	CADTH 2019 conclusion	Current review (2022/2023)	Revised conclusion
manifestations of fluoride toxicity	*No conclusion could be drawn due to significant methodological limitations and lack of statistical analysis.*		association at current North American CWF levels.	*Possible association between fluoride and Loss of appetite, constipation, and fatigue* [22]. • 1 study (N=903, acceptable). *Compared to low-fluoride group, persons in the high-fluoride group reported dyspepsia (75.0%), fatigue (59.4%), and muscle weakness (69.2%)* [82].	association with fluoride exposure.
Other outcomes, suicide	No studies	No studies	N/A	• 1 abstract (N=201, N/A). *Possible association with decrease in suicide rates (insufficient study information)* [5].	Insufficient evidence for an association with fluoride exposure.

Supplementary Material 3. Excluded human studies

This supplement lists all epidemiologic studies identified in the search, but considered ineligible for the systematic review, with reasons provided for exclusion at both level 1 (title and abstract screening) and level 2 (full text examination).

Table 2: Human studies excluded at levels 1 and 2 by reason for exclusion

Level	Reason for exclusion	References
Level 1 *(Title and abstract screening)* *2,202*	Irrelevant exposure (other type of fluoride/water)	821
	Irrelevant population (non-human studies)	798
	Irrelevant outcome	332
	Irrelevant study type (non-original studies)	36
	Irrelevant assessment	63
	Non-recent (prior to 2016)	152
L2 *(Full-text examination)* *422*	Unavailable full-text	29
	Examined in earlier reviews	34
	Irrelevant exposure (other type of fluoride/water)	31
	Irrelevant population (non-human studies)	12
	Irrelevant outcome	98
	Irrelevant study type (non-original studies)	214
	References in non-Latin languages	4

List of excluded studies (arranged by exclusion level, reason for exclusion, then alphabetically by first author's last name)

Level	Bibliography	Reason for exclusion
L1	Abouleish, M. Y. Z. (2016). Evaluation of fluoride levels in bottled water and their contribution to health and teeth problems in the United Arab Emirates Saudi Dental Journal, 28(4), 194-202	Duplicate reference
L1	Alarcón-Herrera, M. T.,Martin-Alarcon, D. A.,Gutiérrez, M.,Reynoso-Cuevas, L.,Martín-Domínguez, A.,Olmos-Márquez, M. A.,Bundschuh, J. (2020). Co-occurrence, possible origin, and health-risk assessment of arsenic and fluoride in drinking water sources in Mexico: geographical data visualization Science of the Total Environment, 698(#issue#), 134168	Duplicate reference
L1	Altine, B.,Gai, Y.,Han, N.,Jiang, Y.,Ji, H.,Fang, H.,Niyonkuru, A.,Bakari, K. H.,Rajab Arnous, M. M.,Liu, Q.,Zhang, Y.,Lan, X. (2019). Preclinical Evaluation of a Fluorine-18 (¹⁸F)-Labeled Phosphatidylinositol 3-Kinase Inhibitor for Breast Cancer Imaging Molecular Pharmaceutics, 16(11), 4563-4571	Duplicate reference
L1	Angulo, M.,Cuitino, E.,Molina-Frechero, N.,Emilson, C. G. (2020). The association between the prevalence of dental fluorosis and the socio-economic status and area of residence of 12-year-old students in Uruguay Acta Odontol Scand, 78(1), 26-30	Duplicate reference

Level	Bibliography	Reason for exclusion
L1	Arnold, W. H.,Gröger, Ch,Bizhang, M.,Naumova, E. A. (2016). Dentin abrasivity of various desensitizing toothpastes Head & face medicine, 12(#issue#), 16-16	Duplicate reference
L1	Athapattu, B. C. L.,Thalgaspitiya, T. W. L. R.,Yasaratne, U. L. S.,Vithanage, M. (2017). Biochar-based constructed wetlands to treat reverse osmosis rejected concentrates in chronic kidney disease endemic areas in Sri Lanka Environmental geochemistry and health, 39(6), 1397-1407	Duplicate reference
L1	Bachanek, Teresa,Hendzel, Barbara,Wolańska, Ewa,Samborski, Dariusz,Jarosz, Zbigniew,Pitura, Karolina Maria,Dzida, Katarzyna,Podymniak, Mariusz,Tymczyna-Borowicz, Barbara,Niewczas, Agata,Shybinskyy, Volodymyr,Zimenkovsky, Andryi (2019). Condition of mineralized tooth tissue in a population of 15-year-old adolescents living in a region of Ukraine with slightly exceeded fluorine concentration in the water Annals of agricultural and environmental medicine : AAEM, 26(4), 623-629	Duplicate reference
L1	Barberio, Amanda M.,Hosein, F. Shaun,Quiñonez, Carlos,McLaren, Lindsay (2017). Fluoride exposure and indicators of thyroid functioning in the North American population: implications for community water fluoridation Journal of epidemiology and community health, 71(10), 1019-1025	Duplicate reference

Level	Bibliography	Reason for exclusion
L1	Barberio, Amanda M.,Quiñonez, Carlos,Hosein, F. Shaun,McLaren, Lindsay (2017). Fluoride exposure and reported learning disability diagnosis among North American children: Implications for community water fluoridation North American journal of public health = Revue 682estizo682ne de sante publique, 108(3), e229-e239	Duplicate reference
L1	Bartos, M.,Gumilar, F.,Gallegos, C. E.,Bras, C.,Dominguez, S.,Monaco, N.,Esandi, M. D. C.,Bouzat, C.,Cancela, L. M.,Minetti, A. (2018). Alterations in the memory of rat offspring exposed to low levels of fluoride during gestation and lactation: Involvement of the alpha7 nicotinic receptor and oxidative stress Reproductive Toxicology, 81(#issue#), 108-114	Duplicate reference
L1	Bondu, J. D.,Selvakumar, R.,Fleming, J. J. (2018). Validating a High Performance Liquid Chromatography-Ion Chromatography (HPLC-IC) Method with Conductivity Detection After Chemical Suppression for Water Fluoride Estimation Indian Journal of Clinical Biochemistry, 33(1), 86-90	Duplicate reference
L1	Bouyeure-Petit, A. C.,Chastan, M.,Edet-Sanson, A.,Becker, S.,Thureau, S.,Houivet, E.,Vera, P.,Hapdey, S. (2017). Clinical respiratory motion correction software (reconstruct, register and averaged-RRA), for ¹⁸F-FDG-PET-CT: phantom validation, practical implications and patient	Duplicate reference

Level	Bibliography	Reason for exclusion
	evaluation British Journal of Radiology, 90(1070), 20160549	
L1	Broadbent, Jonathan M.,Thomson, W. Murray,Ramrakha, Sandhya,Moffitt, Terrie E.,Zeng, Jiaxu,Page, Lyndie A. Foster,Poulton, Richie (2015). Community Water Fluoridation and Intelligence: Prospective Study in New Zealand American Journal of Public Health, 105(1), 72-76	Duplicate reference
L1	Brooks, A.,Jackson, I.,Scott, P. (2017). Evaluation of metal-protein aggregate radioligand [¹⁸F]FL2-b by small animal PET imaging and autoradiography in alzheimer's disease, amyotrophic lateral sclerosis, and lewy body dementia Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI, 58(Supplement 1), #Pages#	Duplicate reference
L1	CADTH (2019). Dental and other health outcomes North American Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports, 10(#issue#), 23	Duplicate reference
L1	Cardenas-Gonzalez, M.,Osorio-Yanez, C.,Gaspar-Ramirez, O.,Pavkovic, M.,Ochoa-Martinez, A.,Lopez-Ventura, D.,Medeiros, M.,Barbier, O. C.,Perez-Maldonado, I. N.,Sabbisetti, V. S.,Bonventre, J. V.,Vaidya, V. S. (2016). Environmental exposure to arsenic and chromium in children is associated with	Duplicate reference

Level	Bibliography	Reason for exclusion
	kidney injury molecule-1 Environmental Research, 150(#issue#), 653-662	
L1	Cárdenas-González, M.,Osorio-Yáñez, C.,Gaspar-Ramírez, O.,Pavković, M.,Ochoa-Martínez, A.,López-Ventura, D.,Medeiros, M.,Barbier, O. C.,Pérez-Maldonado, I. N.,Sabbisetti, V. S.,Bonventre, J. V.,Vaidya, V. S. (2016). Environmental exposure to arsenic and chromium in children is associated with kidney injury molecule-1 Environmental research, 150(#issue#), 653-662	Duplicate reference
L1	Cárdenas-González, Mariana,Jacobo Estrada, Tania,Rodríguez-Muñoz, Rafael,Barrera-Chimal, Jonatan,Bobadilla, Norma A.,Barbier, Olivier C.,Del Razo, Luz M. (2016). Sub-chronic exposure to fluoride impacts the response to a subsequent nephrotoxic treatment with gentamicin Journal of applied toxicology : JAT, 36(2), 309-319	Duplicate reference
L1	Chaitanya, N. C. S. K.,Karunakar, P.,Allam, N. S. J.,Priya, M. H.,Alekhya, B.,Nauseen, S. (2018). A systematic analysis on possibility of water fluoridation causing hypothyroidism Indian journal of dental research : official publication of Indian Society for Dental Research, 29(3), 358-363	Duplicate reference
L1	Chi, Donald L. (2014). Caregivers Who Refuse Preventive Care for Their Children: The Relationship Between Immunization and Topical Fluoride Refusal American Journal of Public Health, 104(7), 1327-33	Duplicate reference

Level	Bibliography	Reason for exclusion
L1	Chiba, F. Y.,Tsosura, T. V. S.,Pereira, R. F.,Mattera, M. S. de L. C.,Santos, R. M. dos,Marani, F.,Garbin, C. A. S.,Moimaz, S. A. S.,Sumida, D. H. (2019). Mild chronic NaF intake promotes insulin resistance and increase in inflammatory signaling in the white adipose tissue of rats Fluoride, 52(1), 18-28	Duplicate reference
L1	Chiotellis, Aristeidis,Sladojevich, Filippo,Mu, Linjing,Müller Herde, Adrienne,Valverde, Ibai E.,Tolmachev, Vladimir,Schibli, Roger,Ametamey, Simon M.,Mindt, Thomas L. (2016). Novel chemoselective (18)F-radiolabeling of thiol-containing biomolecules under mild aqueous conditions Chemical communications (Cambridge, England), 52(36), 6083-6086	Duplicate reference
L1	Choubisaa, S. L. (2018). A brief and critical review of endemic hydrofluorosis in Rajasthan, India Fluoride, 51(1), 13-33	Duplicate reference
L1	Collier, T. L.,Yokell, D. L.,Livni, E.,Rice, P. A.,Celen, S.,Serdons, K.,Neelamegam, R.,Bormans, G.,Harris, D.,Walji, A.,Hostetler, E. D.,Bennacef, I.,Vasdev, N. (2017). Automated radiosynthesis of MK-6240 and validation for human use Journal of labelled compounds and radiopharmaceuticals. Conference: 22nd international symposium on radiopharmaceutical sciences, ISRS, 60(#issue#), #Pages#	Duplicate reference

Level	Bibliography	Reason for exclusion
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L2	Sezgin, B. I.,Onur, S. G.,Mentes, A.,Okutan, A. E.,Haznedaroglu, E.,Vieira, A. R. (2018). Two-fold excess of fluoride in the drinking water has no obvious health effects other than dental fluorosis J Trace Elem Med Biol, 50(#issue#), 216-222	Only dental outcome
L2	Alaska Nurses Association, (2018). An Emerging Threat to Drinking Water and Public Health: Forever Chemicals Alaska Nurse, 69(1), 5-8	Other fluoride/water type
L2	Chang, W.,Wang, L.,Zhang, Y.,Wang, M.,Wang, Y.,Li, P. (2019). A review of sources, multimedia distribution and health risks of novel fluorinated	Other fluoride/water type

Level	Bibliography	Reason for exclusion
	alternatives Ecotoxicology and Environmental Safety, 182 (no pagination)(109402), #Pages#	
L2	Chubaka, Chirhakarhula (2019). Roof Harvested Rainwater in the Adelaide Region, South Australia #journal#, #volume#(#issue#), #Pages#	Other fluoride/water type
L2	Duan, Q ,Li, Y ,Lei, P ,Chen, X ,Guan, Z (2019). Skeletal Features of Children Living in the Area of Coal-Burning Type of Endemic Fluorosis Detected by X-Ray Imaging XXXIVth Conference of the International Society For Fluoride Research, 52(1), 86	Other fluoride/water type
L2	Fan, Z.,Gao, Y.,Wang, W.,Gong, H.,Guo, M.,Zhao, S.,Liu, X.,Yu, B.,Sun, D. (2016). Prevalence of Brick Tea-Type Fluorosis in the Tibet Autonomous Region J Epidemiol, 26(2), 57-63	Other fluoride/water type
L2	Ghosh, S.,Rabha, R.,Chowdhury, M.,Padhy, P. K. (2018). Source and chemical species characterization of PM10 and human health risk assessment of semi-urban, urban and industrial areas of West Bengal, India Chemosphere, 207(#issue#), 626-636	Other fluoride/water type
L2	Guan, Z ,Wang, Y ,Duan, Q,Liu, R ,Li, F,Xu, S ,Yang, G ,Deng, J ,Li, Y ,Wu, C ,Liu, Y We, N ,Dong, Y,Qi, X ,Yu, W (2019). Basic Investigation and Clinic Treatment for the Coal-Burning Type of Endemic Fluorosis in Guizhou, China XXXIVth Conference of	Other fluoride/water type

Level	Bibliography	Reason for exclusion
	the International Society For Fluoride Research, 52(1), 83-84	
L2	Iarc Working Group on the Evaluation of Carcinogenic Risk to Humans (2017). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Some Chemicals Used as Solvents and in Polymer Manufacture, #volume#(#issue#), #Pages#	Other fluoride/water type
L2	Mastrantonio, M.,Bai, E.,Uccelli, R.,Cordiano, V.,Screpanti, A.,Crosignani, P. (2018). Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy Eur J Public Health, 28(1), 180-185	Other fluoride/water type
L2	Medline Plus, (2017). Fluoride #journal#, #volume#(#issue#), #Pages#	Other fluoride/water type
L2	Medline Plus, (2017). Fluoride Overdose #journal#, #volume#(#issue#), #Pages#	Other fluoride/water type
L2	Medline Plus, (2018). Osteosclerosis #journal#, #volume#(#issue#), #Pages#	Other fluoride/water type
L2	Negm, A. M (2017). The Nile Delta #journal#, #volume#(#issue#), #Pages#	Other fluoride/water type
L2	Spitz, J (2019). Genetic, Epigenetic and Environmental Factors: The Triangle of Health XXXIVth Conference of the International Society For Fluoride Research, 52(1), 78-79	Other fluoride/water type

Level	Bibliography	Reason for exclusion
L2	Struneckà, A ,Strunecky, O (2019). Neurotoxicity of Fluoride: Autism Spectrum Disorders XXXIVth Conference of the International Society For Fluoride Research, 52(1), 77	Other fluoride/water type
L2	Davoudi, M ,Mahvi, A H,Barjasteh-Askari, F Bazrafshan, E,Sarmadi, M,Ghorbani, M,Yaseri, M (2019). Relationship of fluoride in drinking water with hypertension prevalence and blood pressure. PROSPERO 2019 CRD42019138629 #journal#, #volume#(#issue#), #Pages#	Research protocol
L2	Frazão, P,Belotti, L (2019). Effectiveness of fluoridation of public water supply in Brazil - systematic review. PROSPERO 2019 CRD42019142050 #journal#, #volume#(#issue#), #Pages#	Research protocol
L2	Rosário, H,Rosário, B,Vieira, W,Cericato, G,Nóbrega, D,Paranhos, L R (2019). External control of fluoride concentration in public water supply in Brazilian cities: a meta-analysis. PROSPERO 2019 CRD42019120870 #journal#, #volume#(#issue#), #Pages#	Research protocol
L2	Alarcon-Herrera, M. T.,Martin-Alarcon, D. A.,Gutierrez, M.,Reynoso-Cuevas, L.,Martin-Dominguez, A.,Olmos-Marquez, M. A.,Bundschuh, J. (2020). Co-occurrence, possible origin, and health-risk assessment of arsenic and fluoride in drinking water sources in Mexico: Geographical data	Used reference concentration

Level	Bibliography	Reason for exclusion
	visualization Sci Total Environ, 698(#issue#), 134168	
L2	Bai, X.,Song, K.,Liu, J.,Mohamed, A. K.,Mou, C.,Liu, D. (2019). Health risk assessment of groundwater contaminated by oil pollutants based on numerical modeling International Journal of Environmental Research and Public Health, 16 (18) (no pagination)(3245), #Pages#	Used reference concentration
L2	Jolović, B.,Stevanović, A.,Nogić, M. (2017). Causes of increased concentration of fluorides in groundwater in Srebrenica municipality Journal of Engineering & Processing Management, 9(1), 69-75	Used reference concentration
L2	Levine, K. E.,Redmon, J. H.,Elledge, M. F.,Wanigasuriya, K. P.,Smith, K.,Munoz, B.,Waduge, V. A.,Periris-John, R. J.,Nalini, Sathiakumar,Harrington, J. M.,Womack, D. S.,Rajitha, Wickremasinghe (2016). Quest to identify geochemical risk factors associated with chronic kidney disease of unknown etiology (CKDu) in an endemic region of Sri Lanka - a multimedia laboratory analysis of biological, food, and environmental samples Environmental Monitoring and Assessment, 188(10), 548	Used reference concentration
L2	Li, Y.,Wang, F.,Feng, J.,Lv, J. P.,Liu, Q.,Nan, F. R.,Zhang, W.,Qu, W. Y.,Xie, S. L. (2019). Long term spatial-temporal dynamics of fluoride in sources of	Used reference concentration

Level	Bibliography	Reason for exclusion
	drinking water and associated health risks in a semiarid region of Northern China Ecotoxicol Environ Saf, 171(#issue#), 274-280	
L2	Odiyo, J. O.,Makungo, R. (2018). Chemical and microbial quality of groundwater in Siloam village, implications to human health and sources of contamination International Journal of Environmental Research and Public Health, 15(2), 317	Used reference concentration
L2	Ranasinghe, N.,Kruger, E.,Chandrajith, R.,Tennant, M. (2018). Groundwater fluoride in Sri Lanka: opportunities to mitigate the risk at maximum contaminant level Ceylon Med J, 63(4), 174-179	Used reference concentration

Supplementary Material 4. Included animal studies

This supplement lists all animal studies eligible for inclusion in the systematic review, categorized by endpoint and tier of relevance. A tiered approach was employed to determine and select studies with key information relevant to the study objectives. This approach categorized studies into three tiers, with tier-1 containing all key information for the review and tier-2 containing supporting information. Studies in tier-1 underwent full data abstraction and quality assessment, as they tended to be guideline studies (according to the Office of Economic Collaboration and Development [OECD] or subject to Good Laboratory Practices [GLP]) that assessed potential health effects via the oral route of exposure at relevant concentrations (≤ 20ppm). A limited data extraction with no quality assessment was performed for studies placed in tier-2. No data abstraction or quality assessment was undertaken for tier-3 studies. To supplement the description of animal evidence in the main manuscript, a longer summary of evidence is included below.

4.1. List of included animal studies, by reported endpoints

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
	n= 0	n= 34	n= 59	n= 46	n= 13	n= 18	n= 7	n= 1	n= 18	n= 11	n= 15	n= 27	n= 5	n= 47
Adedara 2017 [107]					✓							✓		
Ahmad 2012 [108]				✓										
Akimov 2020 [109]														Oxidative stress
Al-Sabaawy 2020 [110]				✓										
Ali 2019 [111]				✓										

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Altindag 2021 [112]				✓										
Altintas 2010 [113]														Oxidative stress
Baba 2016 [114]												✓		
Balaha 2021 [115]													✓	
Balaji 2015 [116]			✓											
Bartos 2018 [117]				✓										
Basha 2013 [118]												✓		
Basha 2011 [119]			✓		✓									
Basha 2011 [120]														Oxidative stress
Basha 2012 [121]														Oxidative stress
Bataineh 2006 [122]														
Bharti 2011 [123]														Oxidative stress
Bharti 2011 [124]														Oxidative stress
Birkner 2006 [125]												✓		Oxidative stress
Blaszczyk 2012 [126]		✓												
Blaszczyk 2009 [127]														Oxidative stress
Bondu 2017 [128]		✓												
Bondu 2019 [129]		✓												

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Bouaziz 2007 [130]														Oxidative stress
Bulduk 2020 [131]							✓							
Cao 2016 [132]				✓										
Cao 2019 [133]			✓											
Cao 2021 [134]			✓											
Cárdenas-González 2013 [135]												✓		
Cenesiz 2008 [136]										✓				
Chaithra 2019a [137]				✓										
Chaithra 2019b [138]				✓										
Chattopadhyay 2011 [139]									✓			✓		
Chaudhary 2010 [140]														Metabolism
Chen 2013 [141]		✓												
Cheng 2008 [142]		✓												
Choudhary 2020 [143]		✓		✓										
Chiba 2010 [144]						✓								
Chiba 2015 [145]						✓								
Chiba 2019 [146]						✓								Metabolism
Chioca 2008 [147]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Chouhan 2013 [148]														Oxidative stress
Chu 2020 [149]		✓												
Das 2006a [150]				✓										
Das 2006b [151]										✓				
de Cássia Alves Nunes 2016 [152]		✓				✓								
Dec 2018 [153]									✓					Oxidative stress
Dec 2019 [154]			✓											
Dey 2021 [155]		✓												
Dhurvey 2016 [156]				✓										
Dong 2015 [157]			✓											
Dong 2017 [158]			✓											
Faruk 2021 [159]					✓									
Feng 2012 [160]														Oxidative stress
Ferreira 2021 [161]											✓			Oxidative stress
Foda 2021 [162]					✓									
Gao 2009 [163]			✓											
Garcia-Montalvo 2009 [164]						✓								
Ge 2018 [165]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Geng 2014 [166]				✓										Oxidative stress
Grucka-Mamczar 2009 [167]														Oxidative stress
Gupta 2016 [168]		✓												
Gupta 2015 [169]		✓												
Gutierrez-Salinas 2010 [170]										✓				
Han 2014 [171]			✓											
Hosokawa 2010 [172]												✓		
Hosokawa 2016 [173]		✓												
Hosokawa 2015 [174]										✓				
Hu 2012 [175]						✓								
Inkielewicz-Stepniak 2012 [176]														Oxidative stress
Interlandi 2018 [177]				✓										
Izquierdo-Vega 2008 [178]				✓										
Jaiswal 2020 [179]			✓											Oxidative stress
Jana 2018 [180]				✓		✓				✓				
Jetti 2016 [181]			✓											
Jiang 2014 [182]				✓										
Jiang 2014 [183]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Kanagaraj 2015 [184]									✓					
Kanbur 2009 [185]														Oxidative stress
Kant 2010 [186]														Blood bio-chemistry
Karadeniz 2008 [187]														Blood bio-chemistry
Kaya 2012 [188]		✓												
Khan 2019 [189]									✓					
Khandare 2011 [190]														
Khandare 2007 [191]						✓								
Kido 2017 [192]												✓		
Kido 2017 [193]												✓		
Kivrak 2012 [194]			✓											
Kobayashi 2014 [195]		✓												
Kobayashi 2011 [196]														Urine analysis
Kobayashi 2009 [197]												✓		
Krishnamoorthy 2015 [198]										✓				
Kuang 2017 [199]										✓				
Leite Ade 2007 [200]											✓			
Li 2017 [201]		✓												

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Li 2019 [202]			✓											
Li X 2021 [203]		✓	✓	✓					✓			✓	✓	
Li Y 2021 [204]		✓								✓				
Liang 2020a [205]				✓										
Liang 2020b [206]				✓										
Lima Leite 2014 [207]						✓								
Liu 2014 [208]			✓											
Liu 2012 [209]					✓									
Liu 2016 [210]					✓									
Liu 2008 [211]				✓										
Liu 2019 [212]										✓	✓			
Liu 2015 [213]				✓										
Liu 2010 [214]			✓											
Liu 2020 [215]											✓			
Liu 2021 [216]				✓										
Lobo 2015 [217]						✓								
Lombarte 2016 [218]						✓								
Lopes 2020 [219]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Lou 2013 [220]			✓											
Lu 2014 [221]				✓										
Łukomska 2020 [222]			✓								✓			
Lupo 2011 [223]						✓								
Ma 2020 [224]		✓												
Madhusudhan 2009 [225]				✓										
Mahaboob Basha 2013 [226]			✓											
Mahaboob Basha 2013 [227]												✓		
Malvezzi 2019 [228]						✓								
Mandic 2020 [229]			✓						✓		✓			
Martin-Pardillos 2014 [230]		✓												
McPherson 2018 [231]			✓		✓									
Miao 2013 [232]									✓					
Min 2021 [233]				✓							✓			
Mohamed 2016 [234]														Oxidative stress
Mrvelj 2020 [235]					✓									
Mujahid 2015 [236]							✓							
Nabavi 2013 [237]												✓		

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Nadei 2019 [238]			✓											
Nageshwar 2018 [239]			✓											
Niu 2009 [240]			✓											
Nkpaa 2018 [241]			✓											
Oka 2020 [242]														Autophagy
Ola-Davies 2018 [243]									✓			✓		Hypertension
Omóbòwálé 2018 [244]							✓							
Oncu 2006 [245]								✓						Lipid
Oncu 2007 [246]				✓							✓			
Oner 2020 [247]									✓					
Owumi 2019 [248]									✓			✓		
Oyagbemi 2018 [249]							✓							Hypertension
Oyagbemi 2018 [250]							✓							
Oyagbemi 2021 [251]				✓			✓				✓			Oxidative stress
Pei 2017 [252]		✓												
Pereira 2011 [253]			✓											
Pereira 2017 [254]		✓				✓								
Perera 2018 [255]									✓			✓		

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Podder 2011 [256]											✓			
Podder 2008 [257]											✓			
Puranik 2015 [258]					✓									
Qing-Feng 2019 [259]			✓											
Radovanovic 2021 [260]			✓						✓	✓	✓			
Raju 2019 [261]			✓											
Raju 2020 [262]									✓			✓		
Ran 2021 [263]			✓											Proteomic, dental fluorosis
Ranjan 2009 [264]									✓			✓		Oxidative stress
Ray 2020 [265]				✓										Oxidative stress
Reddy 2014 [266]														Oxidative stress
Sakallioglu 2014 [267]		✓												
Sanchez-Gutierrez 2019 [268]				✓										
Sarkar 2014 [269]					✓									
Shalini 2015 [270]			✓											
Shankar 2013 [271]		✓												
Shankar 2021 [272]		✓									✓			Serum bio-chemistry
Sharma 2018 [273]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Sharma 2019 [274]				✓										
Sharma 2021 [275]														Bodyweight
Sharma 2021 [276]		✓	✓											Antioxidants, blood bio-chemistry
Shashi 2017 [277]				✓							✓			
Saumya 2017 [278]				✓										
Song 2014 [279]											✓	✓		
Song 2013 [280]									✓			✓		
Song 2011 [281]		✓												
Stawiarska-Pieta 2012 [282]									✓					
Stawiarska-Pieta 2009 [283]														Oxidative stress
Sudhakar 2018 [284]			✓											
Sun 2010 [285]			✓											
Sun 2014 [286]											✓			
Sun 2009 [287]				✓										
Sun 2020 [288]			✓								✓		✓	Antioxidants, stool bacteria
Teng 2018 [289]			✓											
Tian 2019 [290]				✓										
Tian 2019 [291]												✓		

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Trivedi 2012 [292]			✓											
Turkekul 2020 [293]		✓												
Usuda 2016 [294]									✓			✓		
Validandi 2017 [295]						✓								
Vasant 2010 [296]						✓								
Vasant 2012 [297]						✓								
Vasant 2011 [298]						✓								
Wan 2006 [299]				✓										
Wang 2018 [300]				✓										
Wang 2009 [301]					✓									
Wang 2019 [302]													✓	
Wang 2017 [303]				✓										
Wang 2021 [304]			✓								✓			
Wasana 2015 [305]												✓		
Wei 2018 [306]			✓											
Wei R 2016 [307]				✓							✓			
Wei Y 2016 [308]														biomarkers of fluorosis
Whitford 2009 [309]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Wu 2008 [310]				✓										
Wu 2019 [311]				✓							✓			
Xin 2020 [312]			✓								✓			Serum bio-chemistry
Xin 2021 [313]			✓								✓		✓	Serum bio-chemistry, gut flora
Xu 2007 [314]												✓		
Xu 2010 [315]					✓									
Yan 2007 [316]		✓												
Yan 2011 [317]		✓												
Yan 2016 [318]			✓											
Yang 2015 [319]		✓												
Yang 2013 [320]												✓		
Yao 2019 [321]		✓												
Yildirim 2018 [322]							✓		✓			✓		
Yildiz 2006 [323]		✓												
Yu 2013 [324]		✓												
Yu 2019 [325]			✓											
Yue 2020 [326]														Metabolism
Zhang 2020 [327]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Zhang 2013 [328]			✓											
Zhang 2012 [329]										✓				
Zhang 2016 [330]				✓										
Zhang 2013 [331]			✓											
Zhang 2011 [332]			✓											
Zhang 2017 [333]				✓							✓			
Zhang 2015 [334]			✓											
Rui 2017 [335]												✓		
Zhang 2013 [336]				✓										
Zhang 2008 [337]			✓											
Zhao 2017 [338]				✓										
Zhao 2018 [339]				✓										
Zhao 2019 [340]			✓											
Zhao 2021 [341]		✓									✓			Blood bio-chemistry, urine fluoride
Zheng 2016 [342]			✓											
Zhou 2013 [343]				✓										
Zhu 2014 [344]											✓			
Zhu 2011 [345]			✓											

Study	Cancer	Bone / Skeletal	Neuro/ Cognitive	Developmental/ Reproductive	Endocrine including thyroid	Diabetes or Glucose or Lipid Metabolism	Cardiovascular	Respiratory	Hepatic	Immunotoxicity	Genotoxicity	Renal/ Kidney	Intestinal/ GIT	Others
Zigui 2017 [346]			✓											

4.2. Characteristics of the included tier-1 animal studies

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Reproductive toxicity				
Cao 2016 [132]				
Oral (drinking water), subchronic mice study • 8- weeks-old Kunming mice, males only • 10 animals per group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 2, 4, 8 mg/kg bw/day** (0, 11, 22, 44 mg F/ L) • Vehicle – drinking water • 11 weeks of exposure Outcomes assessed • **Reproductive toxicity** • Specific outcomes: - Organ weights (femur, epididymis, testis) - Histological examination of testis	D-R relationship: **increase in all reproductive endpoints assessed with increase in NaF concentration** • Results: - Overall growth: animals in all NaF-treated groups showed poor development, rough coats and even rough teeth with dark brown stains - Bone F levels: significantly increased in all treatment groups - Sperm quality: significant decrease in sperm count and significant increase in the deformity ratio of sperm and sperm head of higher treatment groups (50 and 100 mg/L).	"NaF did have toxic effects on male reproductive system, which reduced the testosterone content and sperm number, and increased the abnormality ratio of sperm and sperm head, supported by the damages of the testicular structure, as a consequence of depressed HSF2 level,	1

[xxxix] When not reported by authors, exposure concentrations (mg/L or ppm fluoride) are converted into doses (indicated with an asterisk '*') using the following default conversion factors, as recommended by Health Canada (1994) 347. Canada H. Human health risk assessment for priority substances. Ottawa, ON: Ministry of Health. Health Canada; 1994.: 1 ppm or mg/L chemical in water equals to 0.14 mg/kg bw/day in rats or 0.20 mg/kg bw/day in mice.

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	- Testosterone concentration in blood and testis - Sperm count - Expression levels of spermatogenesis related genes (qPCR) and proteins (ELISA)	- Testis histology: tissues of all treated mice showed a few vacuoles in seminiferous tubules, irregular arrangement and decreased layers of spermatogenic cells with most obvious damage in 100 mg/L NaF that includes abnormal arrangement and morphological malformations of spermatogenic cells, and decreased number of sperm in the lumen; overall histological examination indicated aggravated testicular tissue damage in all treatment groups. - Testosterone levels in serum and testis: both levels were significantly decreased in higher treatment groups (50 and 100 mg/L). - Gene and Protein expression: the mRNA expressions of spermiogenesis specific genes (Ssty2, Sly, HSF2) corresponding protein levels were changed markedly in higher treatment groups (50 and 100 mg/L).	which resulted in the downregulation of Ssty2 and Sly mRNA and protein."	
Chaithra 2019 [137]				
Oral (gavage), subchronic rat study • Adult Wistar rats, males only • 5 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • 0, 0.45, 2.26, 4.5 mg/kg bw/day • Vehicle – de-ionized water • 52 days of exposure Outcomes assessed	D-R relationship: **increase in several reproductive parameters with increase in dose** • Results: - Body or tissues weights: significant decrease in testis, epididymis and seminal vesicle tissue weight (relative) of 5 and 10 mg/kg bw groups; and decrease in % body weight gain in all treated animals	"Exposure to F-contaminated groundwater affects spermatozoa, steroidogenesis, and spermatogenesis by inducing oxidative stress. The alterations induced by NaF on the	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	• **Reproductive toxicity** • Specific outcomes: - Sperm count, motility, and abnormality - Activity of testicular 3β-hydroxysteroid dehydrogenase (3β-HSDH) - Serum testosterone conc. - Histology of testis (germ cell count in spermatogenesis) - Activity of oxidative stress markers (superoxide dismutase SOD, catalase CAT and malondialdehyde MDA)	- Sperm count: significant reduction in sperm count and increase in abnormal spermatozoa of all treated animals - Testosterone levels: serum testosterone levels were significantly reduced with increase in NaF dose; 3β-HSDH levels were significantly reduced in 5 and 10 mg/kg bw/day groups. - Histology: distorted & shrunken seminiferous tubules and loss of spermatogonial cells with increased severity (complete loss) in highest dosed animals. A significant dose-dependent decrease in counts of various germ cell types of spermatogenesis. - Antioxidant enzymes: significant dose-dependent reduction in testicular SOD and CAT enzymatic levels; significant increase in testicular MDA levels of 5 and 10 mg/kg bw/day groups	male reproductive system are dose-dependent and increased concentration of NaF causes severe damage to the system. Further, the study reveals that F-induced alterations in reproductive system are reversible."	
Chaithra 2019 [138]				
Oral (drinking water and gavage) reproductive/ developmental toxicity rat study • Adult Wistar rats, males only	Exposure • Sodium fluoride (NaF) • **0, 0.7*, 10 mg/kg bw/day** • Vehicle – deionized water • 52 days of exposure Outcomes assessed	D-R relationship: **significant increase in several reproductive parameters at both doses tested** • Results: - Sperm motility: significant decrease in 10 mg/kg bw and 5 mg/L group	"F exposure affected the reproductive performances of male rats. The present study further revealed the fact that F-induced decline in testosterone levels, reduced sperm motility,	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
• 25 animals/ group, 3 groups	• **Reproductive toxicity** • Specific outcomes: - Sperm Parameters - Serum Concentration of Testosterone - Histology of Testis - Fertility indices - Number of pups delivered	- Sperm abnormality: significant increase in NaF 10 mg/kg bw and 5 mg/L group - Serum testosterone concentration: significant decrease in 10 mg/kg bw and 5 mg/L group - Histology of the Testis: distorted and shrunken seminiferous tubules with loss of different stages of spermatogonial cells and Leydig cells, especially in the 5 mg/L group - Fertility indexes: significant decrease in 10 mg/kg bw group - Number of pups delivered: significant decrease in 10 mg/kg bw and 5 mg/L group	and loss of spermatogonial cells affected the reproductive performances of male rats."	
Liang 2020a [205]				
Oral (drinking water) subchronic mice study • 8-weeks old C57BL-6 mice, males only • 10 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 2.2, 4.5, 9 mg/kg bw/day*** (0, 25, 50, 100 mg/L NaF) • Vehicle – deionized water • 90 days of exposure Outcomes assessed • **Reproductive toxicity** • Specific outcomes:	D-R relationship: **higher F doses induced mitochondrial impairment and mitophagy in testicular cells** • Results: - The altered mitochondrial structures in various degrees were observed either in germ cells or Sertoli cells in NaF treated groups. - In spermatogenic cells, the mitochondrial cristae and the membranes of mitochondrion disintegrated in all NaF-treated groups.	"Fluoride can induce mitochondrial impairment and mitophagy in testicular cells, especially in Leydig cells, and PINK1/Parkin mediated mitophagy participants in this process, which will contribute to the mechanisms of F-induced	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	- Mitochondrial structural impairment and mitophagy in mice testes - Expressions of mitophagy key proteins PHB2 and PINK1 in mice testes	- The expressions of PHB2, both in mRNA and protein levels, were increased significantly in testes, especially in the Leydig cells from fluoride-treated groups. - The mRNA expressions of PINK1 increased significantly in the 2.4 mM NaF group. PINK1 protein levels in the 1.2 and 2.4 mM NaF groups with a dose-dependent manner.	male reproductive toxicity."	
Liang 2020b [206]				
Oral (drinking water) subchronic mice study • ICR mice, males only • 10 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 2.2, 4.5, 9 mg/kg bw/day*** (0, 25, 50, 100 mg/L NaF) • Vehicle – deionized water • 8 weeks of exposure Outcomes assessed • **Reproductive toxicity** • Specific outcomes: - testicular morphology - ultra-structure of the sperm - genes expressions of spermatozoa and testis	D-R relationship: **higher F doses caused changes in testicular morphology and ultra-structure of the sperm** • Results: - Testicular morphology: In 25 mg/L group, the intervals among seminiferous tubules were widened; in the 50 and 100 mg/L groups, the pattern of the seminiferous epithelial cells were disordered, the spermatogenic cells at different development stages were reduced and the boundary was blurred, and many spermatogenic cells fell off into the lumen. Vacuolar-like lesions appeared in 100 mg/L NaF group indicating spermatogenesis and sperm structure were affected by fluoride exposure - Ultra-structure of the sperm: No abnormal changes were seen in 25 mg/L group. Fiber sheath was thin and	"In summary, our study revealed that fluoride exposure altered the structures of the fibrous sheathes and axonemal in sperm flagellum via down-regulating the mRNA and protein expression levels of AKAP3, AKAP4, CFAP43, CFAP44, and HYDIN, which provides a new insight of fluorine alters the structure of sperm flagella"	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
		irregular, and defective structure or even multiple fractures were observed in the 50 and 100 mg/L NaF-treated group. mRNA and protein expression levels of Akap3 and Akap4 were significantly decreased in the 100 mg/L group. - Ultra-structure of spermatozoa flagellum axoneme: in the 50 and 100 mg/L groups, the center pairs were irregular and absent, the "9" in the axial filament were not clearly arranged between the outer twinned microtubules, and some microtubules were irregular in shape. The mRNA expressions of Cfap 43, Cfap44 and Hydin were significantly decreased in the testis of mice from 100 mg/L treatment group. - CFAP44 and HYDIN protein levels of testis were significantly decreased in the 50 and 100 mg/L		
Min 2021 [233]				
Oral (drinking water) chronic study: • Male mice • 13 animals per group, 4 groups	Exposure: ● Sodium Fluoride (NaF) ● **0, 2, 4, 8 mg F/kg bw/day** ● Drinking water ● 90 days of exposure **Outcomes assessed:**	**D-R relationship: increase in sperm deformity rate, decrease in sperm survival** • Results: ○ 50 mg/L NaF exposure at 90 days significantly reduced the organ coefficient of testis in mice compared to the control. No significant change in 25 mg/L or 100 mg/L NaF groups	• The reduction of testicular organ coefficients, semen quality, serum testosterone levels, and changes in the testicular microstructure of mice given 50 or 100 mg/L	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	• **Reproductive toxicity** - Organ coefficient of testis - Sperm count and deformity rate - Histopathological analysis - Serum testosterone - Identification of gene expression	○ Sperm count: Significant decrease in sperm counts in 50 mg/L NaF group ○ Sperm deformity: Significant increases in sperm deformity rate in 25, 50, and 100 mg/L NaF groups ○ Sperm viability: Significant decrease in sperm viability in 50 and 100 mg/L NaF groups ○ Serum testosterone: Significant decrease in serum testosterone in 50 and 100 mg/L NaF groups ○ Histopathological changes: the quantity of spermatogenic cells and spermatozoa presented strikingly decreased trend and the gap between spermatogenic tubules increased significantly, especially in 50 and 100 mg/L NaF group ○ Differentially expressed piRNAs: In the 50 mg/L NaF group, there were 1047 up-regulated and 1080 down-regulated piRNAs compared to control ○ Expression analysis: the target genes expression of Ap4e1, Gga2, Gla and Ap1s3 were increased gradually in 50 and or 100 mg/L NaF group	of NaF in water for 90 days showed that these exposures can cause significant testicular damage. Fluoride can induce testicular damage through altered piRNA expression in the testes	
Sun 2010 [285]				
Oral (drinking water) subchronic mice study	Exposure • Sodium fluoride (NaF)	D-R relationship: **Inhibition of sperm hyperactivation in a dose-dependent manner** • Results:	In summary, this study demonstrated that sperm hyperactivation was significantly reduced in	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
• Adult Kunming mice, males only • 60 animals/ group, 4 groups	• **0, 2.84, 6.28, 14.18 mg/kg bw/day** (0, 30, 70, 150 mg/L NaF) • Vehicle – distilled water • 49 days of exposure Outcomes assessed • **Reproductive toxicity** - Sperm quality evaluation and assessment of hyperactivation - Ca2+ concentration ([Ca2+]) in spermatozoa - Gene/protein expression changes in sperm	- Sperm quality: sperm motility significantly decreased by 15.24 and 18.43%, respectively, in 70 and 150 mg/L groups. Sperm count and survival significantly reduced in 150 mg/L group. - Sperm hyperactivation: 70 and 150 mg/L F concentrations significantly inhibited sperm hyperactivation by 21.70 and 29.73%, respectively, showing a dose-dependent manner. - Sperm Ca2+ levels: significant decrease in sperm Ca2+ concentrations by 16.92% and 30.1% in 70 mg/L and 150 mg/L groups, respectively. - A significant reduction in sperm CAMK2, but not in CALM. Protein expression was observed in 70 and 150 mg/L groups	mice administrated with 70 and 150 mg/l NaF in drinking water for 49 days, along with the decreased Ca2+ concentration, CAMK2 protein expression, and CatSper1 mRNA level in sperm. It may be one of the mechanism by which excessive F induced male infertility.	
Sun 2014 [286]				
Oral (drinking water) subchronic mice study • Adult Kunming mice, males only • 20 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 2.84, 6.28, 14.18 mg/kg bw/day** (0, 30, 70, 150 mg/L NaF) • Vehicle – distilled water • 49 days of exposure Outcomes assessed	D-R relationship: **sperm abnormalities were significantly enhanced with increasing NaF concentration** • Results: - Sperm abnormalities: a significant increase in sperm head abnormality was observed in 150 mg/l group; and significant tail abnormality was found in 70 and 150 mg/L group.	In summary, this study presents evidence that NaF adversely affected mice sperm chromatin structure in a dose dependent manner. Reduced P1 and P2 mRNA expression and altered histones and	

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	• **Reproductive toxicity** - Sperm quality, morphology and DNA integrity - Sperm gene and thiol group changes	- Sperm DNA integrity: % DNA denaturation was significantly increased in 70 and 150 mg/L group.	total thiol groups levels could contribute to the sperm damage resulted from F exposure	
Wang 2018 [300]				
Oral (drinking water) subchronic mice study • 30-day old Kunming mice, males only • 10 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 4.52, 9, 13.5 mg/kg bw/day*** (0, 50, 100, 150 mg/L NaF) • Vehicle – water • 90 days of exposure Outcomes assessed • **Reproductive toxicity** - Sperm quality evaluation - Total RNA extraction and quantitative real-time polymerase chain reaction - Immunohistochemistry for CREM and ACT	D-R relationship: **the sperm count and viability and the percentage of malformed sperm were increased in a dose-dependent manner** • Results: - A significant decrease in testis weight was observed in the 100 and 150 mg/L groups; no significant differences in the average epididymis weights - The sperm count and sperm viability were decreased in all F-treated mice and a statistically significant increase in the percentage of malformed sperm was noted in 100 and 150 mg/L groups - Protein expression of CREM and ACT: CREM protein expression levels were significantly decreased in a dose-dependent manner. The protein expression levels of ACT were decreased significantly in all treatment groups	"In conclusion, our results demonstrate that after 90 days of exposure in mice, F impairs sperm quality, which was associated with the downregulation of the testicular transcription factors CREM and ACT. Thus, this could represent one of the molecular mechanisms underlying the effect of F on the male reproductive system."	1
Wei 2016a [307]				

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Oral (drinking water) chronic mice study • Adult Kunming mice, males only • 20 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 2.2, 4.5, 9 mg/kg bw/day*** (0, 25, 50, 100 mg/L NaF) • Vehicle – distilled water • 180 days of exposure Outcomes assessed • **Reproductive toxicity** - Sperm quality - Testicular histopathology - Gene and protein expression analysis (testicular interleukin-17(IL-17), interleukin-17 receptor C (IL-17RC), tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6)) - Concentration of nitric oxide (NO) in testis	D-R relationship: **sperm quality was altered in a dose-dependent manner (between 50 – 100 mg/L)** • Results: - Sperm quality: sperm count, and abnormality were significantly altered with increasing concentrations of NaF at 50 mg/L and above - Testis histopathology: at the 25 mg/L dose, spermatogenic cells changed disorganization and denudation; at the 50 mg/L dose, there were a lot of vacuoles in seminiferous tubules; at the 100 mg/L dose, testicular histological alterations included loss and shedding of sperm cells within the lumen - Gene expression: NaF treatment (100 mg/L) altered mRNA levels of f IL-17, IL-17RC, TNFa and IL-6 but not f IL21, TGF-b and IL-1b. Similarly, IL17 and TNFa protein contents were significantly increased in the testicular fluid of 100 mg/L dose compared to controls - NO levels: a significant increase in iNOS mRNA in 50 and 100 mg/L NaF groups and a significant increase in NO content of 100 mg/L NaF group was observed	Taken together, our results demonstrated that, after 180 days exposure to mice, fluoride could induce testicular toxicity, which was associated with up-regulation of testicular inflammatory mediators including IL-17, TNF-a and NO.	1
Wu 2019 [311]				

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Oral (drinking water) chronic mice study • 8-week-old BLB/c mice, males only • 20 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 2.2, 4.5, 9 mg/kg bw/day*** (0, 25, 50, 100 mg/L NaF) • Vehicle – distilled water • 150 days of exposure Outcomes assessed • **Reproductive toxicity** - Sperm Quality - Testicular Histopathology - Influence on Inflammation Cytokines - Status of Immunocyte and Cytokines in Testis	D-R relationship**: higher F doses altered testicular histology and sperm quality** • Results: - Sperm quality: Sperm motility and viability were significantly reduced in 100 mg/L NaF groups, relative controls - Testicular histopathology: normal histological structure was observed in testis of controls and 25 mg/L group mice. However, a different degree of infiltration status in different immune cells, sloughing of cells and vacuolation of spermatogenic epithelium, a reduction of sperms in seminiferous tubule and significant reduction in spermatogenic score was noted in testis of 50 and 100 mg/L group mice. - Inflammation cytokines: relative controls, expression of IL-6, IL-17A, TNF-α and IFN-γ were significantly increased in 100 mg/L group mice.	Based on this study results, authors confirm that NaF induces adverse effects on testis including testicular inflammation. The presence of specific Antis-perm autoantibodies in anti-testicular auto-antibodies and the notable recruitment of immunocyte, these key factors of autoimmune orchitis, are observed in NaF groups. These results indicate that testicular inflammation induced by excessive F exposure is associated with autoimmune orchitis. And IL-17A is a key cytokine to play an important role in this inflammation.	1

Renal or Kidney Toxicity

Chattopadhyay 2011 [139]

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Oral (drinking water) subchronic mice study • 8 weeks old, Swiss albino mice, males only • 8 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 1.35, 13.5 mg/kg bw/day*** (0, 15 and 150 mg/L NaF) • Vehicle – water • 30 or 90 days of exposure Outcomes assessed • **Hepatotoxicity and Renal or Kidney Toxicity** - Organo-somatic index (OSI) - Liver function tests - Glutathione (GSH) - Glutathione-s-transferase (GST) - Thiobarbituric acid reactive substances (TBARS)	D-R relationship: **severe alteration of renal histological structures, liver enzyme levels in both F treatment groups** • Results: - No death or clinical symptoms; no significant difference in water consumption rate or body weight (weight gain) - No significant difference in the OSI of liver and kidney - Liver function: GPT level increased significantly in all the treatment groups whereas GOT level increased significantly in Gr III (65%) and VI (73%) - GSH-GST response and TBARS production: a significant decrease (32%) in GST of the liver of group II mice; MDA production increased significantly Gr-IV mice. TBARS level increased significantly in the kidneys of Gr-II mice - Histopathology of liver: Gr II mice showed extensive vacuolar degeneration in the cytoplasm and loss of integrity in the epithelium lining of central vein; Gr IV mice showed hepatocellular hypertrophy, cytoplasmic vacuolization and extensive hepatic sinusoidal dilation - Histopathology of kidney: severe alteration of renal histological structures, atrophy of glomeruli, blood-filled	"The present study clearly indicates that F induces hepatotoxicity and nephrotoxicity in mice evidenced by oxidative stress, histopathological changes in the liver and kidney with concomitant effects on normal hepatic function."	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
		spaces and varying degree of degeneration of tubular epithelium were noticed in Gr-II and Gr-IV mice - Heat shock protein 70 profile: elevated expression of Hsp 70 in kidneys of group II and group IV than group III; liver Hsp 70 reduced gradually dose and time dependent manner		
Cárdenas-González 2013 [135]				
Oral (drinking water) subchronic rat study • Weanling Wistar rats, males only • 12 animals/ group, 3 groups	Exposure • Sodium fluoride (NaF) • **0, 2, 7 mg/kg bw/day*** (0, 15, 50 ppm F) • Vehicle – water • 40 days of exposure Outcomes assessed • **Renal or Kidney Toxicity** - Urinary and serum creatinine (Cre) - Urinary glomerular filtration rate (eGFR) - Urinary kidney injury biomarkers: Kim-1, Clu, OPN, B2M and CysC	D-R relationship: **urinary creatinine and several kidney injury biomarkers were altered at highest F doses** • Results: - A small non-significant dose-dependent increase in the serum creatinine levels in 15 and 50ppm groups. - A small non-significant dose-dependent decrease in the eGFR in 15 and 50 ppm groups. - Urinary kidney injury biomarkers: significant increase in Kim-1, Clu, OPN, B2M and CysC in 50ppm group. - mRNA expression: significant increase in levels of Kim, Clu and OPN in the renal cortex in 50ppm group.	In summary, our results revealed that the sub-chronic fluoride exposure at environmentally relevant concentrations induces PT injury. This was clearly demonstrated by the increase of early and sensitive kidney injury biomarkers such as Kim-1, Clu, OPN, Hsp72, B2M and CysC at stages were renal function was not altered.	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	- mRNA expression levels of Kim, Clu and OPN in the renal cortex - Histological analysis	- Histological analysis: fluoride exposure induced tubular injury characterized by tubular flattening, loss of proximal tubule brush border, cell detachment and loss of the tubular epithelium continuity. Tubular flattening was observed in both 15 and 50 ppm groups; additionally, 50 ppm group had tubular cell detachment. There was a non-significant dose-dependent increase in percentage of injured tubules		
Kobayashi 2009 [197]				
Oral (drinking water) subchronic rat study • Weanling Wistar rats, males only • 6 animals/ group, 3 groups	Exposure • Sodium fluoride (NaF) • **0, 0.3, 3 mg/kg bw/day*** (0, 5, 50 ppm NaF) • Vehicle – deionized water • 60 days of exposure Outcomes assessed • **Renal or Kidney toxicity** - Renal histopathology - Proteomics	D-R relationship: **50 ppm F dose induced marked histological changes in kidneys** • Results: - Renal histopathology: No marked abnormal changes were seen kidneys of controls or 5 ppm group rats (except mild vascular congestion in 5 ppm rats). Kidneys of 50 ppm group rats had markedly increased blood vessels, larger glomerular & medullar capillaries engorged with erythrocytes. - Renal proteomic changes: protein levels related to detoxification, metabolism and endoplasmic reticulum were significantly changed in treated rats, especially in 50 ppm group. Between control vs 50 ppm F, and control vs 5 ppm F groups, 12 and 6 differentially expressed proteins were detected, respectively. Six	In summary, the histological analysis revealed no damage in kidneys induced by F, except for a vascular congestion in the high-dose group. The differentially (down-regulated) expressed kidney proteins in F dose groups belong to 3 main functional categories i.e. detoxification-related proteins, metabolism-related proteins and miscellaneous, including	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
		proteins, mainly related with metabolism, detoxification and housekeeping, were successfully identified. At the high F group, pyruvate carboxylase, a protein involved in the formation of oxaloacetate was found to be downregulated, while enoyl coenzyme A hydratase, involved in fatty acids oxidation, was found to be upregulated."	endoplasmic reticulum proteins.	
Wasana 2015 [305]				
Oral (drinking water) chronic mice study • 7-8 months old, ICR mice, females only • 6 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 0.012, 0.35, 2.3 mg/kg bw/day** (0, 0.05, 1.5, 10 mg/L F) • Vehicle – drinking water • 295 days of exposure Outcomes assessed • **Renal/ kidney toxicity** - Gross examination - Kidney histopathology - F content in kidneys	D-R relationship: **no significant changes in any outcomes assessed** • Results: - No treatment related deaths or abnormal behavior or visible signs (appetite, depression, lethargy etc.). - No adverse effect on kidney functions due to treatment as indicated by blood urea nitrogen (BUN) and creatinine blood levels. - F treatment didn't induce any histopathological changes in kidney tissues related to CKD including degeneration, necrosis of glomeruli and tubules, atrophy of glomeruli and glomerular capsules, and tubular dilation with leakage	Based on the absence of abnormal histopathological changes and no significant change in blood BUN and creatinine levels, authors conclude that chronic treatment of mice with F in drinking water, within the concentration range of 0.07–15 mg/L, had no adverse effects on kidneys.	1
Hosokawa 2010 [172]				

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Oral (drinking water) subchronic mice study • ICGN mice (ICR derived animal model for congenital nephrotic syndrome) with blood urea nitrogen (BUN) ≥36.0 mg/dL in were used as animals with impaired kidney function, and healthy ICR mice used as controls with normal kidney function • 11-14 weeks old mice, males only • 3-9 animals/ group, 5 groups	Exposure • Sodium fluoride (NaF) • **0, 5, 10, 20, 30 mg/kg bw/day*** (0, 25, 50, 100 and 150 ppm F) • Vehicle – water • 4 weeks of exposure Outcomes assessed • **Renal/ Kidney toxicity** - Change in body and tissue weights - Change in kidney function measured by blood urea nitrogen (BUN) and creatinine (CRE) levels	D-R relationship: **highest dose tested caused increase in BUN levels of ICGN mice, not in ICR mice** • Results: - 100% of 150 ppm and 40% of 100 ppm ICGN mice were died within 24 days of treatment. No deaths in 150 ppm ICR mice were recorded. - Relative liver weight was significantly decreased in 150 ppm ICGN mice. - Significant increase in BUN levels were measured in 150 ppm ICGN mice only (increases were rapid just prior to death). No increase in lower dose levels or in any ICR mice was noted. - Significant increase in CRE levels of 150 ppm ICGN mice was reported.	In conclusion, all the kidney impaired ICGN mice exposed to 150 ppm F died in less than a month, and the kidney function in this group deteriorated significantly, since the mean values of BUN and CRE in the serum were dramatically increased. No death or alteration in BUN or CRE levels were noted in ICR mice (with normal kidney function) under same treatment conditions. People with renal insufficiently should therefore be careful to avoid excessive exposure to F.	2
Perera 2018 [255]				

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Oral (gavage) subchronic rat study • Adult Wistar rats, males only • 9 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 0.03, 0.3, 1.26 mg/kg bw/day*** (0, 0.5, 5, 20 ppm NaF) • Vehicle – distilled water • 15 or 30 or 60 days of exposure Outcomes assessed • **Hepatotoxicity** - Relative organ weight - Hepatic inflammation - Serum creatinine - Serum AST, ALP, and ALT	D-R relationship: **a dose-response relationship was observed for serum AST and ALP** • Results: - Relative organ weight: no significant difference in the relative kidney and liver weights - Hepatic inflammation: mild portal inflammation with lytic necrosis in 0.5 ppm group, multiple areas of focal necrosis and various degrees of portal inflammation appeared in 5 and 20 ppm groups - Serum creatinine: no difference in 15 and 30 days. Significant increase in 20ppm group after 60 days - Serum AST, ALP, and ALT: serum AST activity was higher in 20 ppm group, no significant differences in serum ALT in 15 and 30 days while significantly higher in 5 ppm and 20 ppm after 60 days	"Fluoride exposure impaired hepatocytes and hepatic function, which was strongly supported by the necrosis and portal inflammation histopathologically and increased serum AST, ALT, and ALP activities. Further, it has been demonstrated that there is a possibility of inducing renal damage by high fluoride levels for longer period of administration due to elevated creatinine levels."	1
Endocrine and thyroid related effects				
Liu 2016 [210]				
Oral (drinking water) chronic rat study • One-month old Wistar rats, males and females	Exposure • Sodium fluoride (NaF) • **0, 0.3, 0.6, 1.26 mg/kg bw/day*** (0, 5, 10, 20 mg/L NaF) • Vehicle – water	D-R relationship: • Results: - Thyroid weight and organ coefficient: no obvious changes.	"Fluoride can damage thyroid structure and function, including thyroid weight and organ coefficient changes, morphological	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
• 20 animals/ group, 4 groups	• 2 or 8 months of exposure Outcomes assessed • **Endocrine and thyroid related effects** - Thyroid weight and organ coefficient - Thyroid tissue morphology - Serum T3, T4, FT3, FT4, and TSH - Apoptosis rate of thyroid cells - GRP78, IRE1, sXBP-1 and CHOP mRNA expression in rat thyroid tissue	- Thyroid tissue morphology: the treatment groups displayed smaller and irregular follicular cavity, or even cell mass without a cavity. Serum T3, T4, FT3, FT4, and TSH: 2 months – No change in serum T3, FT3, and TSH; however, serum T4 and FT4 levels were increased in 10 and 20 mg/L groups. T3/T4 ratios showed a dose-dependent reduction 8 months – No change in serum T3, FT3, T4, and FT4; however, TSH levels were reduced in 10 and 20 mg/L groups. T3/T4 ratios decreased only at in 20 mg/L group. - Apoptosis rate of thyroid cells: no significant changes at 2 months. Higher apoptosis rates at 8 months in all groups. - GRP78, IRE1, sXBP-1 and CHOP mRNA expression in rat thyroid tissue: no significant changes at 2 months. - Higher GRP78, IRE1, sXBP-1, CHOP mRNA at 8 months. - GRP78, IRE1, and CHOP protein expression in rat thyroid tissue: increased in treatment groups.	abnormalities in thyroid tissue, alteration of thyroid hormone levels, and an increased apoptosis rate of thyroid cells. ER stress-induced apoptosis is involved in the damage of rat thyroid cells caused by excess fluoride."	
McPherson 2018 [231]				
Oral (drinking water) chronic rat study	Exposure • Sodium fluoride (NaF) • **0, 1.4, 2.8 mg/kg bw/day*** (0, 10, or 20 ppm F)	D-R relationship: None • Results: - Serum T3, T4, and TSH: no significant differences were observed across groups for serum T3 or T4 or TSH	"Serum triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) levels	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
• GD4 Long-Evans hooded rats, males only • six animals/ group, 4 groups	• Vehicle – drinking water • Varying contents F in diet (a standard diet with 20.5 ppm F or a low F diet with 3.24 ppm F) • Exposure from GD6 through PND56 Outcomes assessed • **Endocrine and thyroid related effects** - Serum T3, T4, and TSH	levels; compared to rats maintained on a standard chow diet, TSH levels were significantly lower in rats maintained on low-F− chow	were not altered as a function of 10 or 20 ppm F− in the drinking water"	
Immunotoxicity				
Gutiérrez-Salinas 2010 [170]				
Oral (drinking water) subchronic rat study • Adult Wistar rats, males only • 25 animals/ group, 3 groups	Exposure • Sodium fluoride (NaF) • **0, 0.124, 6.1 mg/kg bw/day** (0, 1, 50 ppm F) • Vehicle – drinking water • Varying contents (low or high) of protein and calcium in diet • 8 weeks of exposure Outcomes assessed	D-R relationship: **the dose intervals are too large to find a dose-dependent trend – only highest dose showed significant changes** • Results: - Metabolic activity of leukocytes: no significant changes in their metabolic activity in 1 ppm group; 50-ppm dose produced a significant decrease ($p < 0.05$) - Expression of Proteins p-53, bcl-2, and Caspase-3: a statistically significant increase in p53 and caspase-3	"Exposure of rats to NaF modifies the expression of p53, bcl-2, and caspase-3 and causes general metabolic changes to leukocytes, which are indicators of changes to normal pattern of apoptosis"	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	• **Immunotoxicity** • Specific outcomes: - Metabolic activity of leukocytes - Expression of Proteins p-53, bcl-2, and Caspase-3	protein levels of 50 ppm group only. No statistically significant change in bcl-2 expression levels		
Bone/skeletal related toxicity				
Hosokawa 2016 [173]				
Oral (drinking water) subchronic mice study • ICR-derived glomerulonephritis (ICGN) mice, males and females • 5 males and 4 or 7 females/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 5, 10, 20 mg/kg bw/day*** (0, 25, 50, and 100 ppm F) • Vehicle – water • 4 weeks of exposure Outcomes assessed • **Bone/ Skeletal related toxicity** - Microdensitometry examination of the femurs	D-R relationship: **highest test dose induced changes in bone mineral content and bone mineral density of the left femur** • Results: - Microdensitometry of femurs: no significant increase in any bone indexes; bone mineral content and bone mineral density of the left femur from the male ICR 150 ppm group were significantly higher.	"In the present study with mice, 150 ppm of F in drinking water induced bone and dental effects." However, authors note that "work on rodents does not relate to humans because higher levels of fluoride are required to get bone and dental affects similar to those in humans; the ability of rodents to excrete or metabolize F more efficiently than humans are able to explains the discrepancy in the F	3

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
			concentrations that induce osteofluorosis between humans and these experimental animals" and it's worthwhile to examine effects of F on osteofluorosis for a period of more than 2 months.	
Kobayashi 2014 [195]				
Oral (drinking water) subchronic mice study • Weanling mice of 129P3/J and A/J strains, males only • 16 per strain/ group, 3 groups	Exposures • Sodium fluoride (NaF) • **0, 2, 10 mg/kg bw/day*** (0, 10, 50 ppm F**)** • Vehicle – drinking water • 8 weeks of exposure Outcomes assessed • **Bone/ Skeletal related toxicity** - Bone morphology (micro CT analysis) - Bone formation (mineral apposition rate MAR)	D-R relationship: **Dose-specific and strain-specific changes only in proteomics data was noted.** Strain specific, but not dose-specific, changes in bone formation. • Results: - Bone morphology: no significant treatment-related differences in bone mineral density (BMD) or other bone parameters of any bone type (femurs, tibiae and lumbar vertebrae) among all treated groups. - Bone formation: Slight dose-dependent increase in new bone deposition (MAR) was observed only in 129P3/J mice. - Bone modeling: As indicated by plasma ALP activity, no statistical differences were observed among the F treatments for either strain.	F in drinking water for 8 weeks didn't induce any significant changes in BMD or bone modeling of either strain mice.	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	- Bone modeling (Plasma alkaline phosphatase activity) - Proteomics	- Collagen expression: based on western blotting data, no statistically significant differences in collagen type 1 protein levels of femur were found in any treated mice. - Proteomics: Significant changes in several bone proteins (related to osteogenesis and osteoclastogenesis) were found among the F treatment groups within and between each strain indicating an influence of genetic background in bone cell responses to F exposure.		
Song 2011 [281]				
Oral (drinking water) subchronic rat study • Wistar rats, males only • 12 animals/ group, 4 groups **Human spot study:** Eighty-six adult male workers at an aluminum factory in Hubei province, China, without liver, kidney, or bone	Exposure • Sodium fluoride (NaF) • **0, 1.4, 21, 56 mg/kg bw/day*** (0, 10, 150, 400 mg/L F) • Vehicle – water • 15 or 30 or 90 days of exposure • Human study - Age (years), serum F (mg/L), urinary F (mg/L) and air F (mg/m3) of participants in Human study:	D-R relationship: **Serum ALP, BALP and BGP levels were affected at highest dose groups** • Results: - Serum alkaline phosphatase activity: serum ALP was significantly increased in 10 and 150 ppm groups on days 15 and 30, but significantly reduced in the 400 ppm group on day 15 - Serum bone alkaline phosphatase activity: only in the 150 ppm group on day 30 did the vitality of serum BALP showed a significant difference - Serum osteocalcin: the BGP content was lower in 400 ppm group on days 30 and 90; but it was higher in the 150 ppm group on day 90	"In conclusion, changes in serum ALP and BALP activity BGP content are important reference indicators of fluoride exposure. We therefore suggest that serum fluoride, serum ALP activity, and BGP content may be important reference indications of fluoride exposure."	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
related diseases were selected	- Fluoride-exposed (n= 58) 38.35±14.24, 0.46±0.22, 2.72±0.16, 2.08±1.01; - Non-exposure controls (n=28) : 39.70±13.90, 0.16±0.07, 0.63±0.16, 0.10±0.06, respectively. - Spot blood samples Outcomes assessed • **Bone/ Skeletal related toxicity** - Serum alkaline phosphatase (ALP) - Serum bone alkaline phosphatase (BALP) - Serum osteocalcin (BGP)	- In the spot study, the activity of serum ALP and BGP content were higher in the medium working-age group (10 years < working-age ≤ 20 years) than in the short working-age group (≤ 10 years). However, compared with the medium working-age group, the content of BGP was lower in the long working-age group (>20 years).		
Cardiovascular toxicity				
Martin-Pardillos 2014 [230]				
Oral (drinking water) chronic rat study • 2-months old Wistar rats, CKD	Exposure • Sodium fluoride (NaF) • **0, 0.123 and 1.31 mg/kg bw/day** (0, 1.5, 15 mg/L F) • Vehicle – drinking water	D-R relationship: **increased MVC and active calcification of the arteries was found in animals exposed to WHO's recommended F concentration** • Results:	Authors conclude that F significantly increased medial vascular calcification (MVC) in animals with CKD and	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
disease models (5/6-nephrectomized (Nx) or sham-operated controls), males only	• 4.5 months of exposure Outcomes assessed • **Cardiovascular toxicity** - Calcium and phosphate deposits in the heart and complete aorta	- CKD: F treatment influenced CKD of the Nx animals (1.2% Pi in diet); 1.5 mg/L and 15 mg/L group animals had higher urea and creatinine levels than controls and sham-operated rats (1.2% Pi diet). (S-1.2Pi). - Calcification of aortas: Nx animals (1.2% Pi diet) of both 1.5 and 15 mg/L group had calcium accumulation in abdominal and thoracic aorta. These calcified spots or lesions were compatible with stage 2 and stage 3 of vascular calcification in 1.5 and 15 mg/L groups, respectively.	hyperphosphatemia by exacerbating the renal damage; and suggest "adding [F] to municipal drinking water, should be reconsidered and should be replaced by a fluoridation policy based on the health status of individuals."	
Metabolism (diabetes/glucose or lipid metabolism) related-outcomes				
Lupo 2011 [223]				
Oral (drinking water) subchronic rat study • 7-weeks old, Sprague-Dawley rats (with surgically induced renal insufficiency), males only • 4 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 0.14, 0.7, 2.1 mg/kg bw/day*** (0, 1, 5, and 15 ppm F) • Vehicle – drinking water • 60 days of exposure Outcomes assessed • **Metabolism related (diabetes/ glucose or lipid metabolism) toxicity** - Glucose homeostasis	• Results: - Glucose homeostasis: **no significant differences either in glucose plasma levels sham and NX rats or among various F-treatment groups.** No significant change in the values of plasma glucose concentration after 120 min of the glucose load across F-treatment groups. However, plasma insulin levels were significantly increased with F levels in DW - Rate of fluoride uptake by bone tissue: significantly higher in NX rats than in sham-operated rats - Parameters of renal insufficiency: no significant differences in these parameters between NX rats and	The intake of fluoridated water from water supply modifies plasma insulin levels without changes in plasma glycemia, both in controls and in rats with renal disease, after 60 days.	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
	- Rate of fluoride uptake by bone tissue - Parameters of renal insufficiency	sham-operated rats or with different F-treatment levels		
Lobo 2015 [217]				
Oral (drinking water) subchronic rat study • Weanling Wistar rats (diabetic D and nondiabetic ND; diabetes was induced with streptozotocin), males only • 9 animals/ group, 6 groups	Exposure • Sodium fluoride (NaF) • **0, 1.4, 7 mg/kg bw/day*** (0, 10, 50 ppm F) • Vehicle – water • 22 days of exposure Outcomes assessed • **Metabolism (diabetes/ glucose or lipid metabolism) related toxicity** - Insulin tolerance test - Plasma Glucose - Plasma Insulin - Insulin resistance	D-R relationship: **F exposure significantly lowered plasma insulin levels in Diabetic animals, but not in non-Diabetic counterparts, with no dose-response trend** • Results: - Plasma glucose: Plasma glucose concentration was significantly higher in Diabetes animals compared with non-Diabetes animals but was not influenced by the treatment with Fluoride. - Diabetic animals had significantly lower plasma insulin levels compared with non-Diabetic counterparts. Exposure to F did not alter plasma insulin levels in non-Diabetes animals. However, in Diabetes animals, plasma insulin concentrations were significantly reduced upon exposure to F, but no dose-response relationship was observed. - Glucose Disappearance Rate was lower in Diabetic animals compared with their non-Diabetic counterparts, despite the difference being significant only for the animals treated with water containing 0 or 10 ppm	"After 22 days of treatment, no alterations in glycemia, insulinemia, KITT, and HOMA2-IR (homeostasis model assessment 2 of insulin resistance) were seen for ND. F-exposure of D rats led to significantly lower insulinemia, without alterations in glycemia"	2

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
		fluoride. In addition, Kitt was not significantly changed upon exposure to fluoride, both in non-Diabetic and Diabetic animals. - Exposure to F significantly increased %S in Diabetic animals, and this effect was more pronounced for the rats treated with water containing 10 ppm fluoride.		
Malvezzi 2019 [228]				
Oral (drinking water) subchronic mice study • 35–60-day-old non-diabetic (NOD) mice, males only • 8 animals/ group, 3 groups	Exposure • Sodium fluoride (NaF) • **0, 0.9, 4.5 mg/kg bw/day*** (0, 10, 50 ppm NaF) • Vehicle – water • 21 days of exposure Outcomes assessed • **Metabolism related (diabetes/ glucose or lipid metabolism) toxicity** - Evaluation of plasma glucose and insulin levels and insulin resistance (IR) - Proteomic analysis of liver and gastrocnemius muscle	**D-R relationship: Low F exposures reduced plasma glucose levels** • Results: - 10 ppm group had a significant reduction in the plasma glucose levels and a significant increase in the β-cell function (%B). No significant difference among the treatment groups were seen regarding plasma insulin or HOMA2-IR. - Proteomic analysis: in the muscle tissues of 10 ppm F group, increased expression of proteins involved in energy metabolism, and in the 50 ppm F group, increased expression of proteins related to muscle contraction, differentiation of brown adipose tissue and apoptosis were found. Similarly, in the liver tissue of the 10 ppm F group, increase in proteins involved in energy metabolism and protein synthesis, and in the 50-ppm group, proteins	In summary, our results suggest that early treatment with low F concentration seems to prevent or at least delay the onset of T1D, probably by increasing the antioxidant defense. However, it should be noted that despite rodent models have greatly contributed to our understanding of T1D, differences between humans and rodents must be acknowledged when interpreting the	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
		related to ROS metabolism and energetic metabolism were altered. Additionally, western blotting confirmed an increase in isoforms of Glutathione S transferase in 100 ppm group liver tissues.	results obtained using animal models.	
Genotoxicity				
Chattopadhyay 2008 [257]				
Oral (drinking water) subchronic mice study • 2-3 months old, Swiss albino mice, males only • 4-6 animals/ group, 6 groups	Exposure • Sodium fluoride (NaF) • **0, 0.7, 1.4, 2.7, 9, 13.6 mg/kg bw/day*** (0, 7.5, 15, 30, 100, and 150 mg/L NaF**)** • Vehicle – drinking water • 30 or 90 days of exposure Outcomes assessed • **Genotoxicity** - Organ weights - Mitotic inhibition, - Chromosomal aberrations - Chromatid breaks - Femur bone marrow cell count	**D-R relationship: inconsistent** • Results: - No treatment related changes in the percentage of - mitotic indices (MI) of bone marrow cells - a significant increase in the percentage of aberrant metaphases and chromatid breaks in all treatment groups with highest in 15 mg/L group. - The total number of nucleated cells per femur or percentage of bone marrow cells at different phases didn't change across any treatment groups	"F in vivo is actually more genotoxic at certain lower concentrations (15mg/L) than at higher concentrations (100 or 150 mg/L)."	3
Leite Ade 2007 [200]				

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Oral (gavage) acute rat study • Adult Wistar rats, males only • 5 animals/ group, 7 groups	Exposure • Sodium fluoride (NaF) • **0, 10, 20, 40, 60, 80 and 100 mg/kg bw** • Vehicle – deionized water • Single dose (killed after 2 hours of administration) Outcomes assessed • **Genotoxicity** - DNA damage in blood, liver, kidney, thyroid gland and urinary bladder	• Results: - **No DNA damage observed** in blood, liver, kidney, urinary bladder and thyroid gland cells, regardless of the fluoride dose administered.	"In conclusion, even acute lethal doses of fluoride administered to rats were unable to induce genotoxicity in all cell types tested, as depicted by the single cell comet assay. Since DNA damage is an important step in events leading from carcinogen exposure to cancer, this study represents a relevant contribution to the correct evaluation of the potential health risk associated with chemical exposure."	2
Neurotoxicity				
Nadei 2019 [238]				
Oral (drinking water) chronic rat study • PND42 Wistar rats, males only	Exposure • Sodium fluoride (NaF) • **0, 0.7, 2.8, 7 mg/kg bw/day*** (0, 5, 20, 50 ppm F)	D-R relationship: **all three doses caused an impairment in the processes of spatial learning and formation of long-term memory** • Results:	"The results of our work have shown that long-term consumption of excessive F− doses exerts pronounced	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
• 10 animals/ group, 4 groups	• Vehicle – water • 12 months of exposure Outcomes assessed • **Neurotoxicity** - Short-term and long-term memory (using novel object recognition (NOR) test) - Spatial learning and memory (using Morris water maze test) - Expression of Calpain proteins in hippocampus	- Novel object recognition: in 1 hour session, a significant decline in DI (discrimination index), an index of recognition memory, in rats exposed to 50 ppm fluoride was noted; the decline noted in 5 and 20 ppm groups was not statistically significant. In 24 hour after training, the rats from all three fluoride groups were not able to discriminate between new and familiar object, with DI being a few times less than that of control rats for animals given 20 and 50 ppm fluoride. - Morris water maze test: Following everyday training, escape latency substantially decreased in all groups of animals. However, starting from day 3, efficiency for spatial learning was significantly lower for rats in 5 and 50 ppm whereas inconsistent in 20 ppm group. In spatial probe test (day 6), the rats from 20 ppm fluoride group had lesser number of visits to target quadrant and, accordingly, spent less time and swam shorter distance within this quadrant. The distance traveled in target zone by the animals exposed to 50 ppm fluoride was also shorter. No statistical difference in these parameters was revealed for rats from 5 ppm group. - A dose-dependent decline of calpain-1 content in cytoplasm of hippocampus, but significant increase of its expression in membrane fractions in comparison to control	negative impact on cognitive capacities of rats and on their hippocampal cells. Although the formation of short-term memory was sensitive to 50 ppm F− only, all three F− doses induced the deficit of long-term memory." And, "altered expression of signaling molecules of calpain-1 cascade at background of stable activity of calpain-2 and its effectors, observed in rat hippocampus after long-term F− intoxication, suggests the disruption of link between early and late LTP phases, i.e., between induction and consolidation of memory, leading to decline in cognitive capacities of animals."	

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Teng 2018 [289]				
Oral (drinking water) chronic rat study • Weanling SD rats, males only • 13 animals/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 0.9, 1.9, 3.8 mg/kg bw/day*** (0, 15, 30, 60 mg/L NaF) • Vehicle – water • 18 months of exposure Outcomes assessed • **Neurotoxicity** - Ca2+ concentration in rats' hippocampus - CaMKIIα expression - c-fos expression - Histology and Immunochemistry of brain	**D-R relationship:** • Results: - **[Ca2+] increased in all treatment groups**, with significant increases noted in the 30 and 60 mg/L groups - CaMKIIα increased significantly in the 30 and 60 mg/L groups - c-fos increased significantly in the 30 and 60 mg/L groups	"In conclusion, our data showed fluorosis could lead to the enhancement of [Ca2+] and the expression level of CaMKIIα and c-fos in the rat hippocampal CA3 region. The results support the idea that fluorosis can exert neurotoxic effects by changing the [Ca2+] in nerve cells. Calcium overload in the hippocampus may be the initiating factor of neuronal apoptosis induced by fluoride. We deduce that Ca2+/ CaMKIIα/c-fos channel signal may be a molecular mechanism of central nervous system damage induced by chronic fluoride intoxication"	1

Study design	Exposure[xxxix] & Outcomes	Results	Authors' conclusion	Quality
Zhang 2020 [327]				
Oral (drinking water) subchronic rat study • Four-weeks-old SPF-level Wistar rats, males and females only • 10 /sex/ group, 4 groups	Exposure • Sodium fluoride (NaF) • **0, 3.5, 7, 14 mg/kg bw/day*** (0, 25, 50, 100 mg/L F) • Vehicle – distilled water • 90 days of exposure Outcomes assessed • **Neurotoxicity** - Learning Impairment - Neuronal Autophagy	**D-R relationship: An increase in learning impairment with increase in F exposure** • Results: - Learning Impairment ((Morris water maze): the average escape latency had an increasing trend with the increase of fluoride exposure indicating fluoride-induced learning impairment. The escape latency of the rats in the 100 ppm group was significantly longer. - Neuronal Autophagy: the expression of Beclin-1 increased with the concentration of fluoride. Beclin-1 expression was significantly higher in the 50 and 100 ppm group. - Ultrastructural Abnormalities: lipofuscins increased in all groups with an increasing trend with the increase of fluoride exposure. Number of liposomes increased while the number of organelles decreased in the 100 ppm group.	"This study shows that excessive intake of fluoride via drinking water would impair the learning ability of rats. The impairment of the ability of the hippocampus to collect and respond to external information may be related to a large amount of autophagy in the hippocampal CA1 and DG region neuron."	2

4.3. Quality assessment of the included tier-1 animal studies[xl]

Study	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Were there any other potential threats to internal validity	Quality
Cao 2016 [104]	+	NR	++	NR	++	+	+	++	+	1
Cárdenas-González 2013 [106]	+	NR	+	+	+	+	+	+	+	1
Chaithra 2019a [108]	NR	NR	+	NR	+	–	–	++	++	2
Chaithra 2019b [109]	–	NR	NR	NR	++	+	++	++	+	2
Chattopadhyay 2011 [110]	+	NR	++	NR	++	+	+	++	+	1
Gutierrez-Salinas 2010 [134]	+	NR	+	NR	++	+	+	++	+	2
Hosokawa 2010 [136]	NR	NR	+	NR	+	+	+	++	++	2
Hosokawa 2016 173	NR	NR	+	NR	– –	–	+	++	–	3

[xl] Quality of evidence was assessed using the OHAT risk of bias tool

Study	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Were there any other potential threats to internal validity	Quality
Kobayashi 2014 [158]	+	NR	++	NR	++	+	+	++	+	1
Kobayashi 2009 [160]	+	NR	+	NR	+	+	+	++	+	1
Leite Ade 2007 [163]	+	NR	+	++	++	+	+	+	+	2
Li 2021a [203]	+	NR	++	NR	++	+	+	+	+	1
Liang 2020a [166]	+	NR	+	NR	++	–	+	++	+	2
Liang 2020b [167]	+	NR	+	NR	+	–	+	++	+	2
Liu 2016 [171]	+	NR	+	NR	++	+	+	++	+	1
Lobo 2015 [176]	+	NR	NR	NR	–	–	+	+	+	2
Lopes 2020 [219]	+	+	+	+	++	+	+	++	+	1
Lupo 2011 [180]	+	NR	+	NR	+	+	+	++	–	2
Malvezzi 2019 [185]	+	NR	++	NR	+	+	+	++	+	1
Martin-Pardillos 2014 [186]	NR	NR	+	NR	+	–	–	+	–	2

Study	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Were there any other potential threats to internal validity	Quality
McPherson 2018 [187]	+	NR	++	NR	+	++	++	++	++	1
Min 2021 [233]	+	+	++	+	+	–	+	++	+	2
Nadei 2019 [192]	+	NR	+	NR	++	+	+	+	+	1
Perera 2018 [206]	+	NR	+	NR	++	++	+	++	+	1
Podder 2008 [208]	NR	NR	+	NR	+	–	+	++	–	3
Ran 2021 [263]	+	+	++	+	++	+	+	++	+	1
Song 2011 [225]	+	NR	+	NR	++	+	+	++	–	2
Sun 2010 [229]	+	NR	++	NR	++	+	+	++	+	1
Sun 2012 [348]	+	NR	+	NR	++	+	+	++	+	1
Teng 2018 [232]	NR	NR	+	++	++	+	+	++	+	1
Turkekul 2020 [293]	NR	NR	NR	NR	+	+	+	+	+	2
Wang 2018 [300]	+	NR	+	NR	++	–	+	++	+	1
Wasana 2015 [305]	+	NR	++	NR	+	+	++	++	–	1
Wei 2016a [307]	+	NR	+	NR	+	+	+	++	+	1
Wu 2019 [311]	+	NR	++	NR	+	+	+	++	+	1

Study	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Were there any other potential threats to internal validity	Quality
Zhang 2020 [327]	+	NR	+	NR	++	–	+	++	+	2

Legend:	*Definitely low risk of bias*	++	*Probably low risk of bias*	+	*Probably high risk of bias*	– / NR	*Definitely high risk of bias*	– –

4.4. Characteristics of the included tier-2 animal studies

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Owumi 2019 [248]			
Adult male Wistar rats (n=32; 10 weeks old)	Exposure • 0 (corn oil), 15 mg/L NaF (~5mg/kg bw F) in DW • 14 days Outcomes assessed • **Hepatotoxicity and Renal toxicity** • Liver and kidney function (serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH)) • Levels of reactive oxygen (ROS) and nitrogen species (RONS); and antioxidant status of liver and kidneys (activity of superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPx) and GSH) Proinflammatory biomarkers (nitric oxide (NO), myeloperoxidase (MPO), TNF-α and IL-1β) and caspase-3 (CASP3) activity in liver and kidneys • Histopathology of liver and kidney	• F didn't induce any significant changes in body weight or relative tissue weights of liver or kidney • The serum ALT, AST, ALP, and LDH activities were significantly elevated in F-exposed rats • F caused a significant decrease in SOD, CAT, GPx, GST and GSH activities; and significantly increased in RONS and LPO levels in the liver and kidney • F exposure significantly increased the hepatic and renal MPO activity and NO, IL-1β, and TNF-α levels • F treated rats exhibited tubular desquamation, disseminated glomerular congestion with cellular infiltration by inflammatory cells in the kidney; and focal area of necrosis and mild infiltration by inflammatory cells were seen in liver	Rats exposed to fluoride (15 mg/L in drinking water) for 14 days demonstrated hepatorenal toxicity with the decrease in antioxidant enzyme activities, in elevation of ROS & RONS levels and histopathological damage via enhancement of oxido-inflammatory responses and caspase-3.

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Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Podder 2011 [256]			
Male Swiss-albino mice (2–3 months old), 5 mice/group	Exposure • Group I (control): safe drinking water (0.1 mg/L F) Group II: NaF 15 mg /L for 30 days Group III: NaF 15 mg /L for 30 days + safe drinking water for 7 days Group IV: NaF 15 mg /L for 30 days + safe drinking water for 30 days Group V: NaF 15 mg /L for 30 days + safe drinking water for 90 days Outcomes assessed • **Genotoxicity** • Cell death, chromosomal aberrations (Cas) and chromatid breaks	• F-treatment was followed by safe drinking water for different time durations resulted in an increase in percentage of dead cells in bone marrow in groups II–IV compared with the control group • Significant increase in percentage of aberrant cells (cells with chromatid breaks) and chromatid breaks in groups II and III • Compared to group-II mice, group-III and IV showed significant decrease in percentage of aberrant cells and chromatid breaks although their values still remained significantly higher than the control	Treatment with 15 mg NaF/L for 30 days through drinking water followed by substitution with safe drinking water for 30–90 days significantly reduced chromosomal aberrations however these values remained significantly higher than the control group.
Ranjan 2009 [264]			
New Zealand white male rabbits (n=24; 4-6 weeks old); 6/group	Exposure • 0 (control), 50, 100, and 200 mg/L NaF • 90 days Outcomes assessed • **Oxidative stress** • Changes in oxidative stress indices in erythrocytes, liver, and kidneys	Lipid peroxide levels were positively, SOD and CAT levels were negatively correlated with the F exposure in RBC, liver and kidneys.	Excess F exposure is associated with oxidative damage in RBCs, liver and kidney tissues of rabbits.

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Reddy 2014 [266]			
Male Wistar rats (n= 24; 4 months old), 6 per group	Exposure • 0, 20, 60 and 100 ppm • 90 days Outcomes • **Neurotoxicity and Immunotoxicity** • Brain F levels • Neurotransmitter levels in brain • Immunological effects (analysis of CD4 cells, IgG1 & NK cells in rat spleen and blood) • Oxidative stress in brain, blood and spleen	• An exponential increase in brain F content with an increase in F conc in DW • A significant change in various neurotransmitters (epinephrine, histamine, serotonin and glutamate) was observed • A significant dose-dependent reduction in CD4 cells, IgG1, NK of blood and spleen was observed • Similarly, a significant dose-dependent decrease in anti-oxidant enzymes (SOD, GPx, catalase) was noted	At higher exposures, NaF exhibited neuroimmunological and oxidative stress in rats. The results also showed that NaF may cause neurotoxicity.
Shashi 2017 [277]			
Young male Wistar rats; 6 per group	Exposure • 0, 100, 200, and 300 ppm NaF/kg bw/day by oral gavage • 40 days Outcomes assessed • **Reproductive toxicity** • Levels of gonadotropins and reproductive hormones (FSH, LH, testosterone, and intratesticular testosterone levels)	• A significant increase in serum level of FSH, LH; and significant decrease in both serum testosterone and intratesticular testosterone levels were observed at the end of 40 days in all F treatment groups	The present study demonstrates that excess fluoride exposure can induce endocrine hormone disruption over the hypothalamic-pituitary-testis axis by influencing the regulation of reproductive hormones, hence causing deleterious effects on spermatogenesis and

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
			alters sperm and semen quality.
Song 2014 [279]			
Male Sprague-Dawley rats, 12 rats/ group	Exposure • 0, 50, 100, and 200 mg/L of NaF in drinking water • 120 days Outcomes assessed • **Kidney toxicity** • Urinary F levels • Histology of kidneys • Apoptosis and DNA damage in kidneys • Immunohistochemistry of kidneys	• Urine fluoride levels were significantly higher in all of the F treated groups • NaF treated rats showed abnormal pathology in kidneys including hydropic degeneration of epithelial cells of tubule in renal cortex, interstitial fibrosis, chronic inflammatory cell infiltration and structure damage of tubular cells • The percentage of cells in early stages of apoptosis, the percentage of late apoptotic/dead of cells and the percentage of total apoptosis in the kidneys was significantly increased in all F-treated groups • A concentration-dependent increase in % tail DNA, an indicator of DNA damage, was observed	The current study demonstrated that NaF treatment exerts pronounced negative effects on renal cells, including histopathological changes, increased apoptosis, and DNA damage, as well as the increased expression of cytosolic Cyt C and cleaved caspases 9, 8, and 3 protein levels in a dose-dependent manner in rats.
Usuda 2016 [294]			
Male Wistar rats (9-weeks old), 5 per group	Exposure • Control: 0 mg F Low-dose NaF: 2.1 mg F Middle-dose NaF: 4.3 mg F	• Highest change in median UV value was noted in LG-NaF and MG-ZnF2 groups • The median NAG values in the high-dose HG-NaF, KF, and ZnF2 groups showed 2.0,	Our results suggest the leakage of NAG into urine dose-dependent in NaF, KF, and ZnF2. The decline

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	High-dose NaF: 5.4 mg F Low-dose KF: 2.1 mg F Middle-dose KF: 4.3 mg F High-dose KF: 5.4 mg F Low-dose ZnF2: 2.1 mg F Middle-dose ZnF2: 4.3 mg F High-dose ZnF2: 5.4 mg F • Single dose Outcomes assessed • **Kidney toxicity** • Cumulative 24-h urine volume (UV), N-acetyl-β-D-glucosaminidase (NAG), and urine creatinine (Creatu) • Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (Creats)	2.2, and 1.8 times higher than control, respectively ($p < 0.05$ with ≥90th percentile of control) • Highest change in median AST values was observed in MG-NaF and LG-KF groups • The median ALT level of all experimental groups was within the 10th – 90th percentile of controls • Excretion of fluoride was highest in HG-ZnF2 and MG-ZnF2 groups	of GFR for glomerular function disorder was remarkable in the high-dose ZnF2 group, which was placed at the top of the PIM [Probability-Impact Matrix] chart with the highest risk impact factor due to the tubular and glomerular damage it causes.
Wang 2019 [302]			
Female Sprague-Dawley rats (N= 48, 3-weeks-old), 12 per group	Exposure • 0, 25, 50, and 100 mg F/L (NaF salt) • 70 days Outcomes assessed • **Immunotoxicity**	• VH, CD, VH/CD of duodenum, jejunum and ileum were significantly reduced • the content of glycoproteins secreted by the goblet cells of duodenum, jejunum and ileum was significantly decreased in the F 100 group • IL-2, IL-6, TNF-α content was significantly decreased in all treatment groups	Excess F exposure induced morphological changes and immunity in small intestine of rats through decreasing its developmental parameters and the distribution of immune

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• Small intestine morphology (villus height (VH), crypt depth (CD), and villus height to crypt depth ratio (VH/CD)) • Serum cytokine contents (IL-1β, IL-2, IL-6, and TNF-α)		cells, glycoprotein, and cytokine contents in the serum.
Wang 2017 [303]			
Female Kunming mice (30-day old) F0 generation; 21 per group into 4 groups	Exposure • F0 and F1 generation: 0, 50, 100, 150 mg F/L in DW (NaF salt) • 90 days (both F0 and F1 generations) • F0 females mated after 90 days exposure with healthy males by housing at 3:1 ratio F1: healthy F1 generation female mice (4 weeks old); 21 per group into 4 groups Outcomes assessed • **Reproductive toxicity** • Histology and ultrastructural changes in uteri tissues • Expression levels of MMP-9/TIMP-1, a member of matrix metalloproteinases (MMPs) and the tissue inhibitor of matrix metalloproteinases (TIMPs) families	• The rates of pregnancy in the F groups were decreased in a dose-dependent manner • The litter size and birth weight of F1 and F2 mice of both F100 and F 150 group were significantly decreased • Compared to controls, F150 group mice had endometrial epithelial cells irregularly arranged, intercellular space became large, and the boundary of endometrial epithelial cells was not clear; moreover the following ultrastructural changes were observed: vague nucleus, microvilli reduction, increased lysosomes, a dilated endoplasmic reticulum, and mitochondrion vacuolization • the mRNA expression levels of MMP-9 in the F 150 group were consistently increased from the 2nd until the 5th days and then gradually decreased on the 6th and 7th days; similarly, the mRNA expression levels of TIMP-1 were significantly increased and	The results suggest that the excess F exposure in mice for 90 days causes ultrastructural changes in uterii and affect the embryo implantation process via interfering in the MMP-9/TIMP-1 system; may also reduce litter size in female mice.

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
		peaked on the 5th day. Also, corresponding protein levels of MMP-9 and TIMP-1 were significantly increased in the F 150 group on the 3rd and 5th days	
Wei 2016b [308]			
Wistar rats; 5 per sex per group	Exposure • 0, 50, 150, 250 mg/L NaF • 24 weeks Outcomes assessed • **Serum proteomics** • Serum protein expression profiles	• Expression levels of A2M, C4BPA, ORM1, C9, KNG2, SERPINA3N, CP, HPX, HP, and KNG1 showed an increasing trend in the 50 mg/L group, and in contrast decreasing trend in the 150 and/or the 250 mg/L group. Five proteins (A1BG, RGD1564515, F1LN61, F1LM30, and F1LPQ6) revealed a decreasing trend in the 50 and 150 mg/L groups • Most differentially expressed proteins belonged to: inflammatory response (46.9%), response to wounding (53.1%), acute inflammatory response (37.5%); suggesting inflammation and immune reaction proteins were involved in the pathogenesis of fluorosis.	The serum protein expression profile of F-treated mice suggests that the low-dose NaF may promote complement, inflammation, and immune responses, whereas moderate- and high-dose NaF may inhibit these responses; and the proteins identified in this study may serve as biomarkers for fluorosis.
Yan 2007 [316]			
Female B6 and C3H inbred mice	Exposure • 0, 50, 100 ppm F (NaF salt)	• Significant increase in bone fluoride content with increasing fluoride exposure, in both strains of mice	This study demonstrates that increasing F doses at physiological levels has

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
(3-weeks old); 6 mice per group	• 3 weeks Outcomes assessed • **Bone/skeletal related toxicity** • Bone F content • Osteoclastogenesis and hematopoietic colony-forming cell assays • Biomechanical testing of bones	• No change in serum osteocalcin levels in neither strain • In C3H mice, significant increase in osteoclast potential was correlated with: increased F exposure, serum PTH, serum RANKL, serum OPG, serum TRAP5b and bone osteoclast numbers • Tibia trabecular bone quantity and architecture were significantly different between the different F treatment groups for B6 mice only; No significant changes in femur cortical bone were observed between the F treatment groups for either mouse strain	strain-specific effects on bone physiology in mice such as the increase in intact PTH, changes in osteoclastogenesis and increase in CFU-M (monocyte/macrophage), CFU-GM (granulocyte and macrophage), and CFU-GEMM (multipotential) suggesting a role of F in the early stage of osteoclastogenesis.
Yan 2016 [318]			
Adult Wistar rats (5-weeks old); 10 per sex per group	Exposure • 0, 60, 120 ppm F (NaF salt) • 10 weeks Outcomes assessed • **Neurotoxicity** • F content in serum and brain • Ultrastructural changes in brain • Apoptosis in neurons • Bax and Bcl-2 Expressions in the Brain	• Dose-dependent increases of F levels in serum and brain tissues • In 60 ppm group, brain cells appeared cytomorphotic, with intranuclear heterochromatin margination condensation, mitochondrial outer membrane: part vague, rough endoplasmic reticulum: gently expanding, cellular membrane: part swollen. In 120 ppm group, brain cells appeared obviously intranuclear heterochromatin margination aggregated, cellular membrane	Based on the current results, the authors conclude that fluoride exposure induces neuron apoptosis and expression of inflammatory factors by activating microglia in rat brain.

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• Inflammatory factor expressions in the Hippocampus and Cortex region	dissolved, with shrinkage of nuclear and cell volume, organelle dissolved, and apoptosis presented • Apoptotic cells (TUNEL-positive staining) increased with increasing fluoride concentrations • A dose-dependent correlation between expression of Bax and fluoride concentration and a negative correlation was found between Bcl-2 expression and fluoride concentration in the cortex • Indexes of Bcl-2/Bax in the hippocampus significantly lower than the control group, suggesting apoptosis in brain cells	
Zhao 2017 [339]			
Healthy Wistar pregnant rats; 11 per group	Exposure • 0, 1500 mg/L (prior to delivery all rats received distilled water alone; after delivery, maternal rats were given either 0 or 150 mg/L NaF continued to male puppies (same as to their maternal rats) after their weaning (3 weeks old) for 15 weeks) • 15 weeks Outcomes assessed	• An increasing trend in femur F content with an increase in duration of exposure • Sperm count and motility were significantly decreased in treated rats with exposure duration • In treated rats, the seminiferous tubules of each age were reduced in terms of diameter and thickness; the sperm cells were lost and shedding and finally disappeared after 9 weeks	NaF exposure altered organ coefficient, sperm quality, total protein content of testis and testicular histology, as well as the mRNA and protein expression levels of HSP27, 79, 90 and HSF in the testis of rats with an increase in the femur fluoride concentration. In

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• **Reproductive toxicity** • Femur fluoride determination • Organ coefficient of the testes and epididymis • Sperm quality evaluation • Testis histology • Immunohistochemical analysis of testis for expression of HSP27, HSP70, HSP90 and HSF	• Testicular morphological abnormalities were increased with exposure duration in treated rats • The relative mRNA expression levels of HSP27, 70, 90 and HSF in treated rats' testes were significantly changed	addition, in terms of HSPs, significant differences following NaF exposure were observed in the puberty.
Zhou 2013 [343]			
Sexually mature (8-10 weeks old) SD rats, females only 20 animals/ group, 4 groups	Exposure • 0, 100, 150, 200 ppm NaF in water • 6 months of exposure Outcomes assessed • **Reproductive toxicity** - Fertility assessment - Relative weights of reproductive organs - Histopathological examination - Serum hormones - Immunohistochemistry	• Successful pregnancy: rates of successful pregnancy was declined in a dose-dependent manner • Organ coefficients: The ovarian organ coefficients were statistically lower in all treatment groups and the uterine organ coefficients increased statistically in 150 and 200ppm groups. • Serum hormones: Serum E2, P, and LH levels decreased in all treatment groups; serum T levels were statistically lower in100 and 200 ppm groups; serum FSH levels were statistically lower in 50 and 200ppm groups. • Uterine histology: the endometrial cells became larger, and the endometrial glands	"In the present study, we demonstrated the following results. (1) The fertility of female rats may be inhibited after NaF exposure. (2) The secretion of E2, P, T, LH and FSH was suppressed in rats exposed to NaF. (3) NaF exposure decrease d ovarian and uterine weight. (4) The structures of the ovary and uterus were damaged in NaF-treated rats. These results indicate that the reproductive function of

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
		became hypertrophic. Blood vessels in the myometrium had altered shapes and sizes. • Ovarian histology: the total number of each type of follicle decreased in all treatment groups.	female rats exposed to NaF is inhibited. The possible mechanism underlying NaF-induced fertility reductions is as follows: NaF hinders reproductive hormone synthesis and secretion, weakening its ability to regulate the ovary and maintain pregnancy. The ovarian and uterine structures may also be destroyed by NaF."
Adedara 2017 [107]			
Adult male Wistar rats (8 weeks old) group size 8	Exposure • 0, 15 mg/L • 45 days of exposure Outcomes assessed • **Renal toxicity** • Oxidative damage and Thyroid dysfunction: glutathione, malondialdehyde, superoxide dismutase, catalase, glutathione-S-transferase, glutathione peroxidase	• Decreased glutathione, malondialdehyde, superoxide dismutase, catalase, glutathione-S-transferase, glutathione peroxidase	Chronically exposed to NaF induced renal toxicity in rats by increasing oxidative stress indices, decrease of antioxidant enzyme activities, and the functional status of the thyroid system

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Ahmad 2012 [108]			
Male albino mice (3–4 months old) group size: 10	Exposure • 0, 50 ppm • 10 days of exposure Outcomes assessed • **Reproductive toxicity** • Toxicity in testis	• Loss of interstitial tissue, spermatogonia, and spermatogenesis. • Decrease in the average number of spermatogonia perspermatic cord. • Decline in the mean cross-sectional area (CSA) of the seminiferous tubules, whereas increase in the mean CSAs of spermatogonia and primary spermatocytes. • Decline in head length, breadth, tail length, and the length and diameter of the middle part of sperm.	NaF induced steroidogenesis and spermatogenesis in males
Baba 2016 [114]			
Wistar rats weighing, group size: 6	Exposure • 0, 1ppm, 10ppm • 28 days of exposure Outcomes assessed • **Renal toxicity** • Levels of glutathione, malondialdehyde, superoxide dismutase, catalase, glutathione-S-transferase, glutathione peroxidase	Increases in plasma protein, blood urea nitrogen, and creatinine levels	Concurrent exposure to fluoride increased the extent of renal damage, which is due to increased free radical formation and a reduced function of the antioxidant system in renal tissue.
Basha 2011 [119]			

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Adult albino Wistar rats, male 200–250 g, female 170–200 g, group size: 8	Exposure • <1 ppm, 100 ppm, 200 ppm • Exposure through gestation period Outcomes assessed • **Endocrine and Thyroid related toxicity** • Serum thyroid hormones, brain histopathology, and learning memory: serum thyroid hormones (FT3 and FT4), acetylcholine esterase activity, spatial learning and memory	• Decreased serum-free thyroxine (FT4) and free triiodothyronine (FT3) levels and decreased acetylcholine esterase activity. • Presence of eosinophilic Purkinje cells, degenerating neurons, decreased granular cells, and vacuolations in discrete brain regions. • Poor acquisition and retention and higher latency In the T-maze experiments.	Fluoride ingestion continuously through multiple generations induced generational or cumulative effects on the development of the offspring.
Bondu 2017 [128]			
Male Sprague-Dawley rats ≈ 200g, group size 6	Exposure • <1 ppm, 15ppm, 50 ppm • On Vitamin D deficient (test groups) and adequate (control groups) diet • 180 days of exposure Outcomes assessed • **Renal or Kidney Toxicity** • serum osteocalcin, parathyroid hormone, C terminal telopeptide of type I collagen, creatinine, Cystatin C, bone mineral density	• Increased Alkaline Phosphatase and Osteocalcin • C terminal telopeptide levels increased with moderate fluoride exposure and decreased with high fluoride exposure	High fluoride intake deteriorates renal tubular function
Bondu 2019 [129]			

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Male Sprague–Dawley rats, group size 6	Exposure • <1 ppm, 15ppm, 50 ppm • On Vitamin D deficient (test groups) and adequate (control groups) diet • 210 days of exposure Outcomes assessed • **Bone/ skeletal related toxicity** • bone damage: serum total 25OHD, PTH, Osteocalcin, CTx, ALP, calcium, phosphorus and creatinine, albumin, fluoride and urinary cystatin C. • Bone Mineral Density (BMD) and Bone Mineral content (BMC)	• Increased BMD, serum ALP, bone fluoride content, Osteocalcin, and urine fluoride in both control and test groups with increase in F concentration • Mild thickening and increased osteoid in 80% of the Vitamin D deficient rats. • Fluoride deposited in rat bone affects both osteoblastic and osteoclastic activity	Fluoride deposits in bone and affects bone remodeling.
Bulduk 2020 [131]			
Sprague Daley rats weighing 200-250 g (4 groups of 10 females, and 4 groups of 10 males)	Exposure • Groups of n=10 • 0 mg/L of NaF and 0 mg/L of resveratrol (control), 10 mg/L of NaF, 50 mg/L of resveratrol, 10 mg/L of NaF and 50 mg/L of resveratrol • 90 days of exposure Outcomes assessed • **Cardiovascular**	• For each gender, the most marked elevations in the blood pressures were seen in the NaF group. • In both the male and female groups, the chronic administration of resveratrol with NaF led to decreased blood pressures. • The contraction response resulting from phenylephrine administration was increased in the groups administered NaF, whereas it	Resveratrol provides a protective effect against the increased blood pressure caused by NaF and the potential endothelial damage. The protective effect of resveratrol results from its capability to reduce fluorine induced oxidative

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• The effect of resveratrol therapy on the contraction-relaxation responses of the thoracic aorta rings and, on the blood pressure of rats exposed to chronic fluorosis • Serum fluorine level • Blood pressure • Contraction response	was decreased in the groups administered NaF and resveratrol.	stress and endothelial tissue damage.
Cao 2019 [133]			
APP/PS1 double-transgenic mice, B6.Cg-Tg (APPswe, PSEN1dE9) with a 85Dbo/Mmjax background, 3 months old, both male and female, group size 10	Exposure • 100 mg/L, 1000mg/L • 84 days of exposure Outcomes assessed • **Neurotoxicity** • Morris water maze test of spatial learning and memory • Senile plaques, ionized calcium binding adaptor molecule 1 (Iba-1), and complement component 3 (C3) expression, Aβ42, synaptic proteins and enzymes that cleave APP, malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px).	• Decline in learning and memory in shorter time. • Increased senile plaques and level of Aβ42, Iba-1, and BACE1, while reducing the level of ADAM10 in their brains. • Decreased synaptic proteins and enhanced oxidative stress in the hippocampus of APP mice.	Exposure to fluoride, even at lower concentration, can aggravate the deficit in learning and memory and neuropathological lesions of the mice that express the high level of APP.
Chaudhary 2010 [140]			

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Adult male albino rats, group size 10	Exposure • 14.29 mg/L • 30,45,60 days of exposure Outcomes assessed • **Diabetes/ glucose or lipid metabolism related toxicity** • Enzyme profile and lipid profile: serum ALT, AST, LDH, total cholesterol, triglycercide, LDL, HDL, VLDH	• Increase in serum AST and ALT. • Increase in serum total cholesterol, LDL, VLDL, TG, and decrease in HDL.	Fluoride exposure increase serum AST, ALT, total cholesterol, LDL, VLDL, TG, and decrease in HDL
Chen 2013 [141]			
8-weeks-old male Sprague–Dawley rats (weighing 200–210 g), group size 6	Exposure • 20 mg/L • 84 days of exposure Outcomes assessed • **Bone/ skeletal related toxicity** • Bone health: bone mineral density, biomechanical test of femur	• Slightly increased vertebral bone mineral density • Negatively affected bone biomechanical property and bone microstructure.	Fluoride slightly increased vertebral bone mineral density but negatively affected bone biomechanical property and bone microstructure.
Choudhary 2020 [143]			
Swiss albino female mice. Four groups of eight animals each	Exposure • Group 1: 0 ppm NaF • Group 2: 100 ppm NaF • Group 3: 250 ppm NaF • 18 days exposure	• Significant decrease in maternal bodyweight in 100ppm and 250 ppm groups • Significant differences in live fetuses, dead fetuses, fetal weight and fetal size in NaF groups compared to the control	• -"NaF treated mice showed decrease in weight as compared to control"

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	Outcome assessment: • **Bone/Skeletal related toxicity** Skeletal examination • Reproductive toxicity Fertility tests: number of implantations, number of resorptions, number of viable fetuses and dead fetuses, number of stunted fetuses, maternal body weight and placental • Other: Weight, fetal body weight and size.	• Reduced ossification, higher prevalance of rib defects, and skeletal malformation in NaF treatment groups	• -"Number of dead fetuses in high dose of NaF treated group got increased when compared to the control group" • -"The treatment of NaF in this study also affected the average body weight of pups and the placental weight." •
Chu 2020 [149]			
Male BALB/c mice (4 weeks old, n=64), 16 mice/group	Exposure • 0 (control), 25, 50, and 100 mg F/L • 3 months of exposure Outcomes assessed • **Bone/skeletal related toxicity** • Bone histopathology • Dental fluorosis • Bone F concentration • Serum biomarkers (ALP, OCN) for bone differentiation	• In the high F group, tibial trabecula enlarged and merged into large pieces with the adjacent bone trabeculae, F increased cancellous bone formation, and there was thickened cortical bone in the femur of mice exposed to F, especially in high F group • Prevalence rates of dental fluorosis in the three fluoride groups were 43.75% (25 mg F/L), 93.33% (50 mg F/L) and 100% (100 mg F/L). Mice in high F group showed	"[F]luoride up-regulates the expression of Wnt/b-catenin signal transduction molecules and Runx2, contributing to aberrant osteoblasts activity and osteogenesis, and b-catenin plays a pivot role in fluoride-induced viability and

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• Protein expression in bone tissue (Wnt/b-catenin signaling pathway)	severe dental fluorosis, characterized by white spots, cloudy splotches and pitting • There was a dose-dependent positive association with F concentration in drinking water and F in spinal bone. • Serum concentrations of ALP and OCN (biomarkers of bone differentiation) were increased in middle and high F groups • Wnt3a (ligand of Wnt/b-catenin signaling pathway) was significantly up-regulated in the 50 and 100 mg/L F- groups. F gradually increased the protein expression of Gsk3b phosphorylation, b-catenin and its downstream target gene Runx2, which was accompanied by translocation of b-catenin into the nucleus induced by fluoride. F exposure was correlated with increased Wnt3a, b-catenin, the ratio of p-Gsk3b (Ser9) to Gsk3b and Runx2 protein levels	differentiation of osteoblasts."
Dey 2021 [155]			
Male Swiss albino mice (n=54, ~ 20g, 1 month old), 9 mice/group	Exposure • Group I (control): < 0.5 ppm F • Group II: 6.8 ppm F for 4 months • Group III: 6.8 ppm F for 8 months	• Teeth whitening distinctly evident after 1 month of F treatment. In group II, complete whitening of lower incisors was observed after 4 months of F treatment. Teeth became chalky white with enamel erosions after 8 months of treatment in group III.	"[P]rolonged exposure to environmentally relevant concentration of F accumulates in the teeth and bone leading to development of dental and

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• Group IV: 6.8 ppm F for 4 months, then fresh drinking water (containing < 0.5 ppm of F) for next 4 months • Group V: 6.8 ppm F for 4 months, then drinking water (containing < 0.5 ppm of F) supplemented with calcium and vitamin D (2.5-g calcium kg−1 diet and 1000 IU vitamin D kg−1 diet) for next 4 months • Group VI: 6.8 ppm F and supplemented with calcium and vitamin D (2.5-g calcium kg−1 diet and 1000 IU vitamin D kg−1 diet) for 4 months • 4-8 months of exposure Outcomes assessed • **Bone/skeletal related toxicity** • Dental fluorosis • Skeletal fluorosis • Bone elemental content • F content in bone • Behaviour • Locomotion	• Groups II and III exhibited osteosclerosis/increased hardening of the bone. Mild calcification of pelvic bone was observed in group III. • F exposure significantly decreased Ca, Zn, Mn, K, Ni, and S levels in the bone while increased magnesium Mg and Fe was observed. In Group IV, Ca, Zn, Mn, and K levels increased compared to Groups II and III. • F content in the bone was significantly higher in all treated groups, except in group V where F content was comparable to control group levels. F content was highest in group II, followed by group III, VI, and IV. • No signs or symptoms of behavioral changes. • Mice in groups II and III showed slight restrictions in activities like walking and movement of the head and limbs. Changes in locomotion were not observed in other groups.	skeletal fluorosis." Exposure to F altered the metal profile of bone and worsened skeletal health.
Dhurvey 2016 [156]			
Adult female albino rats,	Exposure	• Reduced body weight in the rats ingesting 10, 15, and 20 mg NaF/kg bw/day	Exposure of female albino rats to NaF in drinking

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
weighing about 180–200 g, group size 6	• 0, 5, 10, 15, and 20 mg NaF/kg body weight/day • 30 days of exposure Outcomes assessed • **Reproductive toxicity** Estrous cycle and ovarian hormones: serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen	• Reduced ovarian weight in the rats ingesting 15 and 20 mg NaF/kg bw/day. • Increased duration of the proestrous phase in the 10, 15, and 20 mg NaF/kg bw/day group. • Decreased diestrous, estrous, and metaestrous phases in the 15 and 20 mg NaF/kg bw/day groups. • Decreased hormonal concentrations of luteinising hormone in the 15 and 20 NaF/kg bw/day groups, follicle-stimulating hormone in the 10, 15, and 20 NaF/ kg bw/day groups, and estrogen in the 10, 15 and 20 NaF/kg bw/day groups.	water might have some immediate harmful effects on the reproductive system.
Ferreira 2021 [161]			
Female pregnant wistar rats (n=6, 150-200 g, 90 days old) and their male offspring (sample size not reported)	Exposure • 0 (control), 10, 50 mg F/L • 42 days of exposure Outcomes assessed • **Mechanistic** • F plasma concentrations • Oxidative stress • BDNF expression in hippocampus • Hippocampal proteome	• F exposure increased plasma F concentration in treatment groups compared to control group • Oxidative biochemistry analyses showed that F caused a decrease of ACAP in 10 mg/L group and in 50 mg/L group compared with control group. There was also a marked increase in MDA levels and nitrite levels for both treated groups.	"Exposure to both F concentrations during pregnancy and lactation increased the F bioavailability, triggered redox imbalance featured by a decrease of ACAP, increase of LPO and NO−2 levels, BDNF overexpression and

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
		• mRNA analysis of whole hippocampus indicated that there was an increase BDNF expression in both exposure groups compared to controls. • In the 10 mg F/L group, there were changes in proteins associated to axogenesis, positive regulation of neuron projection development, glycolytic process and regulation of calcium ion transport. In the 50 mg F/L group, proteins associated with morphogenesis of neuronal projection processes, regulation of neuron projection development, axogenesis, glycolytic process and regulation of ERK 1 and 2 cascade.	changes in the hippocampus proteome."
Geng 2014 [166]			
female Sprague-Dawley rats, group size 10	Exposure • 100 or 200 mg/L • 180 days of exposure Outcomes assessed • **Reproductive toxicity** Female fertility: ovarian apoptosis, ROS, SOD, CAT and GSHPx activities and MDA content	• NaF induced ovarian apoptosis, with concomitant activation of oxidative stress. • Exposure to NaF activated extracellular regulated protein kinase (ERK) and c-Jun NH2 kinase (JNK), disrupting the ERK and JNK signaling pathways, while p38 and PI3K remained unchanged	Oxidative stress may play a key role in NaF-induced ovarian dysfunction by activating the apoptotic ERK and JNK signaling pathways.
Hosokawa 2015 [174]			

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
4–5-weeks-old male BALB/c mice weighing 23.2±0.2 g, group size 6	Exposure • 1, 5, 25, and 125 ppm • 30 days of exposure Outcomes assessed • **Immunotoxicity** Immunotoxic effects: TNFα, IL-1β, β-actin, IFN-γ and IL-2	• Reduced intake of food or water per body weight in the 125-ppm group. • Reduced relative weights of spleens in the 1- and 5-ppm groups. • Decline in mRNA expression of TNFα in the macrophages in the 125- ppm group.	The F concentration in the blood in this study may not be sufficiently high (as in vitro studies) to affected mRNA expression in vivo.
Inkielewicz-Stepniak 2012 [176]			
Wistar Han rats (6-weeks old male and female rats weighing ~220 and ~170 g), group size 10	Exposure • 0, 12 mg/L • Days of exposure not reported Outcomes assessed • **Hepatic and renal toxicity** Liver and kidney function: nitric oxide level, thiobarbituric acid reactive substances, advanced oxidation protein products, total antioxidant status, glutathione, protein content in post nuclear supernatant fractions of the liver and kidney	• Fluoride enhanced oxidative and nitrosative stress in investigated tissues. • No gender difference was observed.	F enhanced oxidative and nitrosative stress in investigated tissues.
Kaya 2012 [188]			
Tuj sheep weighing 31±2 kg, group size 10	Exposure • 4 ppm • 270 days of exposure	• Decreased serum PTH levels • Increased serum CT levels	Fluorosis in sheep incurred a decrease in the PTH levels and an

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	Outcomes assessed • **Bone/skeletal related toxicity** • Calciotropic hormone: serum parathyroid hormone (PTH) and calcitonin (CT) activity levels		increase in the CT levels, which may be the result of a temporary rise in serum Ca.
Khan 2019 [189]			
Weanling male A/J and 129P3/J mice	Exposure • 15ppm, 50ppm • 42 days of exposure Outcomes assessed • **Hepatotoxicity** Liver proteome profiles	• Fold change in liver proteins more pronounced in lower F treatment group. • Most of the proteins with fold change upon treatment with 15 ppm F were increased in the A/J mice compared with their 129P3/J counterparts. • Most proteins with fold change were decreased in the A/J mice compared with their 129P3/J counterparts, upon treatment with 50 ppm F.	Male A/J mice attempt to fight the deleterious effects of F at low concentration. A/J animals have higher susceptibility to the deleterious effects of F.
Kido 2017a [192]			
11–12-weeks-old ICR-derived glomerulonephritis (ICGN mice), male ICR mice, group size 5	Exposure • 0, 50, 100, and 150 ppm • 28 days of exposure Outcomes assessed • Renal/ Kidney toxicity	• For the ICGN mice, at the end of the experimental period, BUN in the 150 ppm group was significantly higher than 0 and 50 ppm groups • For the ICR mice, after 3 days, the BUN in the 150 ppm group was higher than the 0 and 100 ppm groups.	Serious toxic effects of ≥100 ppm F in the drinking water for mice with impaired kidney function.

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• Renal function: blood urea nitrogen (BUN), the serum creatinine (CRE), the level of urinary protein, and the creatinine clearance		
Kido 2017b [193]			
6-weeks-old male Sprague-Dawley rats with unilateral ureteral obstruction opertaion, 250–280 g, group size 13	Exposure • 0, 75, and 150 ppm • 14 days of exposure Outcomes assessed • Renal/ Kidney toxicity: transforming growth factor beta 1 (TGF-β1) transcription	Increase in areas or number of cells that stained with Masson trichrome, or with antibodies against collagen type I, alpha-smooth muscle actin (α-SMA, a myofibroblast marker), ED1, ED2, and ED3 (macrophage markers), and TGF-β1.	M2 macrophage-TGF-β1-fibroblast/myofibroblast-collagen synthesis pathway is related to fluoride exacerbated tuburointerstitial nephropathy from UUO.
Kuang 2017 [199]			
ICR mice, group size 60	Exposure • 0, 12, 24, 48 mg/kg bw/day • 42 days of exposure Outcomes assessed • **Immunotoxicity** • Splenic development: splenic growth index, histopathological lesions, T and B-cell subsets and CD4+/CD8+ ratio, cytokine expression levels, IgA, IgG, and IgM contents, cyclins/cdks protein expression	• Decline in growth index and lymphocytes in the white and red pulp • Increased cell percentages of the G0/G1 phase and decreased cell percentages of the S phase • Decline in T cells and B cells as well as IgA, IgG, and IgM contents. • Decreased expression levels of cytokines including interleukin-2 (IL-2), transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and cyclin (E/D and CDK2/4	NaF in 12 mg/kg and over causes toxic effects on the splenic development in mice. Cell cycle arrest is the molecular basis. Cellular and humoral immunity were imparied due to the reduction of T,

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
		• Increased protein expression level of interleukin-10 (IL-10)	B cell numbers and activities.
Leite Ade 2007 [200]			
male Wistar rats with 75 days and weighing approximately 270 g, group size 5	Exposure • 0, 10, 20, 40, 60, 80 and 100 mg/Kg bw/day • 2 hours of exposure Outcomes assessed • **Genotoxicity** DNA damage	No change in the level of DNA strand breaks in all organs at all doses in the mean tail moment.	Oral exposure to NaF did not result in systemic genotoxic effect in multiple organs related to fluoride toxicity
Li 2017 [201]			
3-weeks-old male C57BL/6 mice, group size 10	Exposure • 0, 100mg/L • 105 days of exposure Outcomes assessed • **Bone/ skeletal related toxicity** Bone homeostasis: bone osteoclasts numbers, osteoclasts ultrastructure, osteoclastogenesis, NFATc1 and ATP6v0d2 mRNA expression in osteoclasts	• Impaired bone resorption. • Decline in mRNA expression of nuclear factor of activated T-cells 1 (NFATc1), ATPase H+ transporting V0 subunit D2 (ATP6v0d2) and osteopetrosis-associated transmembrane protein 1 (Ostm1)]	The consumption of fluoride resulted in severe fluorosis and in an impaired OC function.
Lima Leite 2014 [207]			

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Male Wistar rats (60 days old), group size 6	Exposure • 0, 10, or 50 ppm • 22 days of exposure Outcomes assessed • **Diabetes/ glucose or lipid metabolism related toxicity** Diabetes: protein functions and protein interaction	• Quantitative intensity analysis of the proteomic data revealed differential expression between diabetic/nondiabetic rats, and between different F concentrations. • The GO annotations with the most significant terms were muscle contraction, carbohydrate catabolic processes, generation of precursor metabolites and energy, NAD metabolic processes and gluconeogenesis. • Proteins with fold changes interacted with GLUT4. GLUT4 interacting proteins, such as MDH and the stress proteins HSPB8 and GRP78, exhibited decreased expression when D animals were exposed to F.	The presence of the two stress proteins indicates an increase in insulin resistance, which might worsen diabetes.
Liu 2012 [209]			
SD rats 4 weeks old, group size 20	Exposure • 0, 50mg/L, 100mg/L, and 200mg/L • 150 days of exposure Outcomes assessed • **Endocrine and Thyroid related toxicity** Thyroid function: structural changes in the thyroid gland, expression of vascular	• Increased average relative weight of the thyroid glands. • Proliferation and dilatation of capillary blood vessels enlarged follicles with excessive colloid, and obvious nodules in the thyroid glands. • Increased expression of VEGF mRNA in the thyroid gland and the serum NO levels.	Abnormal expression of VEGF induced by fluoride can lead to the proliferation of vascular endothelial cells in the thyroid gland.

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	endothelial growth factor (VEGF) mRNA, expression and deposition of VEGF	• Increased deposition of VEGF in epithelial and follicular cells of the thyroid gland.	
Liu 2020 [215]			
Four-week-old male Wistar rats (20 rats per group, 4 groups)	Exposure • 0, 25mg/L, 50mg/L, and 100mg/L of NaF • 12 weeks of exposure Outcomes assessed • **Bone/Skeletal** • Skeletal fluorosis • Kidney and small intestine were isolated for detection of Klotho with immunohistochemistry (IHC). • Femoral artery blood was sampled to measure the serum levels of sKlotho.	• Urine fluoride concentrations showed a dose-dependent and statistically significant increase in different fluoride-exposed groups, compared to control group. • The ratio of 2-degree and 3-degree dental fluorosis increased with increasing levels of fluoride exposure. • In rats, serum sKlotho levels was significantly higher in F-exposed groups than that in the control group. • Immunohistochemistry results showed that the Klotho expression in the kidney and small intestine increasedwith increased doses of NaF treatment	Urine fluoride concentrations, 2nd and 3rd-degree dental fluorosis, serum sKlotho levels, and sKlotho expression in the kidney and small intestine showed a dose-dependent increase
Lu 2014 [221]			
Kunming male mice (8 weeks old, weighing about 20 g), group size 65	Exposure • 0, 50, 100, 150 mg/L • 56 days of exposure Outcomes assessed • **Reproductive toxicity**	• The percentage of chemotactic sperm decreased with NaF in a dose-dependent manner. • Decreased Ca2+ concentration and AC content In the 100 and 150 mg/L groups.	Excessive fluoride adversely affects sperm chemotaxis. The alteration of Ca2+ concentration, AC content and CatSper1 mRNA expression level may play

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	Sperm chemotaxis: sperm chemotaxis, Ca2+ concentration, adenylate cyclase (AC) content and mRNA expression of mACIII, mACVIII, Golf alpha, CatSper1, CatSper2	• Decreased mRNA expression of CatSper1 in the 100 and 150 mg/L groups.	a key role in the mechanism underlying the affection.
Ma 2020 [224]			
male Wistar rats (3 weeks old; weighing 114.8–180.0 g), group size 20	Exposure • 0, 25, 50, or 100 mg/L • 30 or 90 days of exposure Outcomes assessed • **Bone/ skeletal related toxicity** • Skeletal fluorosis: expression and DNA methylation level of the promoter region off Bone Morphogenetic Proteins (BMP)-2 and BMP-7	• Increased protein expression of BMP-2 and BMP-7 in plasma at 1 month and 3 months. • Increase in BMP-2 expression with an increase of fluoride exposure time. • Hypomethylation was observed in 2 CpG sites (CpGs) of BMP-2 and 1 CpG site of BMP-7 promoter regions.	Fluoride has a dose-response effect on BMP-2 in fluorosis rats, and fluoride-induced hypomethylation of specific CpGs may play an essential role in the regulation of BMP-2 and BMP-7 expression in rats.
Miao 2013 [232]			
male Sprague-Dawley rats (weight = 70–90 g), group size 10	Exposure • <0.1, 50 mg/L • 180 days of exposure Outcomes assessed • **Hepatotoxicity** Liver function: apoptosis and Fas/FasL expressions	• Increased protein and mRNA levels of Fas, and FasL. • Decreased activity of GSH-Px, and SOD. • Increased activity of MDA.	Fluoride induced apoptosis in the liver, thereby causing liver damage in the rats.
Mrvelj 2020 [235]			

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
Twenty male Sprague-Dawley rats. Four groups of two to seven animals per group	Exposure and Outcomes: • Group 3 received 1.2 ppm F drinking water, Group 4 received 0 ppm water. Groups 1 and 2 were not relevant. • 4 weeks exposure Outcomes assessed: • **Endocrine toxicity** - Dark and light cells per unit area in pineal gland - Total cell numbers in pineal gland	• Pineal glands from Group 3 showed significantly fewer cell counts than Group 4 in both light and dark cells	"In sum, our findings suggest that the removal of dietary fluoride promotes growth of the pineal gland in aged rats. This growth initially involves an increase in supporting cell numbers, followed by subsequent increases in the numbers of both light and dark pinealocytes."
Oka 2020 [242]			
C57BL/6 mice (10-week-old, male, body weight 29.4 ± 0.8 g), 2 groups of 6 animals per group.	Exposure • 0 (control), 5 mM NaF treated group • 46 weeks of exposure Outcomes assessed • **Mechanistic** Cell viability and cell apoptosis after exposure to NaF	• Reduced expression of Osterix and Runx2 • The expression levels of ATG5 and Beclin1 were both suppressed by 5 mM NaF in cementoblasts and in periodontal ligament cells • 5 mM NaF induced a high expression of the HIF1-a/p- NFkB axis, which suppressed autophagy and promoted apoptosis. • Treatment with 5 mM NaF enhanced the alveolar bone resorption in both the upper jaw and the lower jaw compared to the control group induced the expression of	• 5 mM NaF reduces autophagy in cementoblasts and increases the expression of HIF-1α. • The oxidative stress activation by 5 mM NaF was also observed with the suppression of autophagy through 5 mM NaF-mediated apoptosis.

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
		Cathepsin K and RANKL in periodontal tissues • Upregulated the expression of autophagy related proteins (ROS, p-NFkB, HIF1-a), suppressed the expression of cementoblast markers and induced apoptosis via the downregulation of ATG5 and Beclin1 expression.	• Decreased levels of autophagy-related proteins in cementoblasts and the periodontal ligament after 5 mM NaF ingestion. • The inhibition of cell proliferation and increased apoptotic rates after treatment with 5 mM NaF suggests that excessive NaF may be cytotoxic. • 5 mM NaF-treated autophagy was not su□cient to counteract the NaF-induced cellular damages in HCEM2 cells
Sanchez-Gutierrez 2019 [268]			
Male CD-1 mice aged 45 days old, group size 6	Exposure • 0, 45.2 mg/L • 60 days of exposure Outcomes assessed	• Decreased sperm quality (motility, viability, and concentration).	Subchronic fluoride exposure of mice with STZ-induced diabetes aggravated testicular

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
	• **Reproductive toxicity** Spermatozoa Quality, Spermatozoa Mitochondrial Membrane Potential, Caspase 3/7 Enzymatic Activity, Histology Analysis	• Spermatozoa presented a significant decrease in ψm and a significant increase in activity caspase 3/7. • Decreased urinary fluoride excretion.	damage and the spermatozoa function.
Zhang 2013 [336]			
Oral (drinking water) subchronic mice study • Adult Sprague-Dawley rats, both sex • 20 animals/sex/ group, 4 groups (male offspring = 5/group)	Exposure • Sodium fluoride (NaF) • **0, 2.2, 4.5, 9 mg/kg bw/day*** (0, 25, 50, 100 mg/L NaF) • Vehicle – distilled water • From pre-pregnancy to PND 56 Outcomes assessed (in male offspring) • **Reproductive toxicity** • Specific outcomes: - Testicular Histopathology - Testicular ultrastructure - Germ cell apoptosis - Oxidative stress markers in testis (MDA and SOD activity)	D-R relationship**: higher F doses altered testicular histology** • Results: - Testicular histopathology: the testes showed atrophy of seminiferous tubule, injury of spermatogonia and decrease of spermatocytes, as well as absence of elongated spermatids in the severely damaged seminiferous tubules, indicative of impaired spermatogenesis and loss of germ cells in 50 and 100 mg/L groups; - Testicular ultrastructure: many spermatogonia and spermatocytes displayed the characteristic features of apoptosis, including condensation and margination of nuclear chromatin in 50 and 100 mg/L groups - Germ cell apoptosis: TUNEL-positive cells were notably increased in testes of 50 and 100	Authors conclude that "developmental exposure of rats to fluoride results in testicular ER stress and inflammatory response, as well as oxidative stress and germ cell apoptosis, with defects in spermatogenesis and accompanying decrease in germ cell count. Furthermore, the present study has also provided important new insights into the roles of ER stress and inflammation in the aggravation of testicular damage.".

Study Design	Exposure & Outcomes	Results	Authors' Conclusion
		mg/L NaF; apoptotic cells accounted for degenerating spermatogonia and spermatocytes - Oxidative stress markers: marked increase of MDA levels in the 50 and 100 mg/L groups; significant reduction in enzymatic activities of SOD in all treated groups	

4.5. Summary of evolving animal evidence

The current review search identified new animal evidence relating to twelve primary endpoints, updating the evidence reported in previous authoritative reviews of animal studies: Health Canada 2010 [1] and the NTP 2020 draft report [103] on neurocognitive outcomes. A summary of evidence for each outcome, based on the most recent critical review and the current review, is provided in the following sections, with emphasis on effects occurring at or below exposures (i.e., 20 ppm) relevant to current fluoride levels in North American drinking water.

Neurological and cognitive outcomes

Summary based on the NTP 2020 draft report [103]: NTP systematically reviewed experimental animal studies published up until 2019 that investigated the effect of fluoride on neurodevelopmental and cognitive outcomes with priority given to learning and memory. This review also focused on mechanistically linked outcomes such as measures of thyroid function. Each included individual study was assessed for study quality using OHAT risk of bias tool. This review concluded that the evidence based on experimental animal studies was ‘inadequate’ to assess whether exposure to fluoride could affect learning and memory, particularly at human-relevant exposure levels. The primary rationale provided for this conclusion was “the inability to separate the learning and memory effects from the effects on motor activity or motor coordination”. The majority of the studies were of poor quality in which either the assessment of learning and memory was not accompanied with evaluation of motor activity to determine whether the observed changes in learning and memory could be due to motor dysfunction or to determine whether results had been affected by adverse effects on general health [349]. However, those studies that did examine both cognitive and motor deficits, “mainly found an association between fluoride exposure and both types of neurological outcomes or found no effect of fluoride exposure on either type of neurological outcome irrespective of the dose range or duration of dosing”.

Current review evidence synthesis: In the current review, a total of 3 low risk-of-bias studies with at least one test concentration ≤20 ppm (tier-1 study) and published since 2019 were identified. Although one study [238] found an impairment in the processes of spatial learning and memory in rats from long term fluoride exposure at 50 ppm, it possesses the same study limitations (i.e., no concurrent assessment of motor activity) identified in studies reviewed in the draft NTP 2020 [103]. Two other low risk of bias tier 1 studies found no significant effects below 20 ppm [219, 263].

Endocrine including thyroid outcomes

Summary based on Health Canada 2010 report: No studies were found examining adverse effects on thyroid at exposure concentrations below 20 ppm. Only studies under very high fluoride exposures (600 mg/L) and/or iodine imbalance (excess or deficiency) conditions were identified.

Current review evidence synthesis: A total of two low risk-of-bias tier-1 studies [210, 231] that assessed changes in thyroid related to fluoride exposure at or below 20 ppm fluoride in drinking water were identified. Both studies were conducted in rats (Wistar or Long-Evans hooded) with exposure concentration ranging from 2.3 to 20 ppm fluoride and for 2 to 8 months. One study [231] did not find a significant association between increase in fluoride concentration (up to 20 ppm) and change in thyroid hormone levels (TSH, T3, or T4); the other study [210] reported statistically significant – though inconsistent across two time points – changes in thyroid hormonal levels (serum T4 increased at 2 months but not at 8 months; serum TSH unchanged at 2 months but decreased at 8 months; serum T3 unchanged; apoptosis of thyroid cells increased) in rats exposed to 4.5 and 9 mg/L fluoride. Additionally, one tier-2 study [107] found significant decline in plasma T3 and T4 levels in rats exposed to 15 mg/L fluoride for 45 days.

Current review evidence synthesis: Overall, the studies included in the current review suggest no or inconsistent evidence of thyroid dysfunction in animals exposed to fluoride in drinking water at concentrations relevant to current fluoride levels in North American drinking water.

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Renal or Kidney related outcomes

Summary based on Health Canada 2010 report: No studies found examining adverse effects on kidney at exposure concentrations below 20 ppm. Wistar mice exposed to very high fluoride concentrations (226 mg/L) during pregnancy through to the 14th day post-delivery demonstrated increase in urinary fluoride excretion (mothers and pups), increase in plasma creatinine and decrease in urinary creatinine levels.

Current review evidence synthesis: Six low to medium risk of bias animal studies [135, 139, 172, 197, 255, 305] were identified that evaluated fluoride effects on kidney function at test concentrations 20 ppm or below. These studies investigated the impact of fluoride exposure in rodents (mice or rats) at different exposure durations (chronic or sub-chronic) given a range of drinking water fluoride concentrations (ranged from 0.05 – 150 mg/L); specific outcomes measured include kidney dysfunction markers such as blood urea nitrogen (BUN) or creatinine (CRE) levels or histological analysis. Three out of six studies found some histopathological changes in kidneys (such as proximal tubule injury) but none reported any significant changes in kidney dysfunction markers such as BUN or CRE at or above test concentrations relevant to humans; except one study [255] found slight but significant increase in CRE levels after long term exposure at 20 ppm fluoride concentrations.

Reproductive/ Developmental outcomes

Summary based on Health Canada 2010 report: Numerous good quality animal studies reported adverse effects on reproductive function however these effects occurred only at very high concentrations that are not relevant to current fluoride levels in North American drinking water or at levels that known to cause dental and/or skeletal fluorosis. Further, high quality multigeneration guideline studies did not find effects on reproductive function from continuous exposure to fluoride in drinking water.

Current review evidence synthesis: Twelve low to medium risk-of-bias tier-1 studies were identified that evaluated adverse effects on reproductive system in experimental animal studies from fluoride exposure at or below 20 ppm [132, 137, 138, 205, 206, 233, 285, 286, 300, 307, 311, 337]. These studies reported that fluoride exposure could induce changes in the organ coefficient of the testis, sperm count, sperm abnormalities, sperm motility, sperm survival, sperm hyperactivation, fertility, testosterone levels, testicular histology and fertility indices. These effects were observed at a range of fluoride exposure concentrations (5 – 100 ppm fluoride in drinking water), different exposure durations (49 to 211 days) and in multiple rodent species (rats and mice); only one study examined effects from exposures during premating, mating, gestation. The lowest concentration tested showing significant reduction in sperm quality was 5 mg/L fluoride. Overall, there was evidence of effects on male fertility, primarily decrease in sperm quality and increased testicular damage, from fluoride exposures at concentrations relevant to current fluoride levels in North American drinking water.

Cancer

Summary based on Health Canada 2010 report: In a cancer bioassay, no malignant tumors related to fluoride exposure were observed, in Sprague-Dawley rats or CD-1 mice exposed to 25 mg/kg bw/day NaF for 95-99 weeks, or in F344 rats exposed to 250 mg/L NaF.

Current review evidence synthesis: No animal studies evaluating the association between fluoride exposure and cancer outcomes were found.

Skeletal/bone related outcomes

Summary based on Health Canada 2010 report: In a comprehensive chronic toxicity/ carcinogenicity bioassay, with F344/N rats and B6C3F1 mice exposed to drinking water containing up to 75 mg/L NaF for 2 years, the estimated NOAELs were 2.7

and 4.1 mg/kg bw/day for the female and male rats, respectively, and 5.7 and 4.9 mg/kg bw/day for the female and male mice, respectively.

Current review evidence synthesis: Three low risk-of-bias tier-1 studies [173, 195, 281] were identified to assess the bone/skeletal related toxicity of fluoride exposure at or below 20 ppm fluoride in drinking water. Hosokawa et al. 2016 [173], reported no significant increase in any bone indexes in male and female nephrotic mice model (ICGN) exposed to NaF for 4 weeks. Kobayashi et al. [195] reported that fluoride in drinking water for 8 weeks did not induce any significant changes in bone mineral density or bone modeling. Song et al. [281], reported increase in serum ALP, but no change in serum bone alkaline phosphatase activity, in Wistar rats exposed to 10 ppm fluoride for 15 and 30 days. Turkekul et al. [293] reported severe thinning of the epiphyseal growth plate and trabecular thickness, as well as fat accumulation in the bone marrow in a dose-dependent manner (5-50 ppm fluoride). In a few tier-2 studies, rats and mice exhibited, upon long term (84-210 days) fluoride exposure (15-50 ppm fluoride), elevated bone mineral density and serum ALP and worsened skeletal health (osteosclerosis, mild calcification of pelvic bone) [128, 129, 141, 155].

Diabetes or Glucose or Lipid Metabolism related outcomes

Summary based on Health Canada 2010 report: No animal evidence on diabetes, or any metabolism related outcomes occurred at or below 20 ppm fluoride exposure concentrations was identified.

Current review evidence synthesis: Three low risk-of-bias tier-1 studies [217, 223, 228] were identified to assess association between diabetes or any metabolism related outcomes and fluoride exposure at or below 20 ppm fluoride in drinking water. Lupo et al. 2011 [223], reported that intake of fluoridated water from water supply (up to 15 ppm for 60 days) modified plasma insulin levels without affecting plasma glycaemia in Sprague-Dawley rats. No change in glycaemia, insulinemia, KITT, and HOMA2-IR were found in Wistar rats exposed to 10 ppm NaF for 22 days [217]. In another study [228], non-diabetic mice exposed to 10 ppm NaF had a significant reduction in the plasma glucose levels and a significant increase in the β-cell function.

Cardiovascular outcomes

Summary based on Health Canada 2010 report: In a multigeneration rodent study, Wistar rats exposed to 0.45, 4.5, 22.5, 45 mg/L in drinking water showed significant histopathological changes in the myocardial tissues (at ≥ 22.5 mg/L) accompanied by increase in markers of oxidative stress such as superoxide dismutase, GSH peroxidase, and catalase.

Current review evidence synthesis: The single tier-1 study identified [230] in this review found that after being exposed to NaF for up to 15 mg/L for 4.5 months, Wistar rats with chronic kidney dysfunction had significantly increased medial vascular calcification (MVC). No experimental studies on animals with normal kidney function were identified. In one tier-2 study [131] an observed increase in blood pressure and potential endothelial damage occurred at 10 mg NaF/L in healthy Sprague Dawley rats.

Respiratory outcomes

Summary based on Health Canada 2010 report: No animal evidence on respiratory outcomes were identified.

Current review evidence synthesis: No tier-1 or tier-2 study was identified.

Hepatic system related outcomes

Summary based on Health Canada 2010 report: No animal evidence on hepatotoxicity was identified.

Current review evidence synthesis: Two low risk-of-bias tier-1 studies [139, 255] were identified to assess the hepatotoxicity of fluoride exposure at or below 20 ppm fluoride in drinking water. Chattopadhyay et al. 2011 [139], reported increasing GPT level, decreasing GST levels, and extensive vacuolar degeneration in the cytoplasm and loss of integrity in the epithelium lining of central vein, on 8 weeks old Swiss albino mice, exposed at 15ppm NaF exposure for 30 to 90 days. Perera et al. 2018 [255], reported a dose-response increase in serum AST and ALP on male adult Wistar rats, exposed to up to 20 ppm NaF for 60

days. Another tier-2 study, Owumi et al. [248], showed that male Wistar rats exposed to fluoride (15 mg/L in drinking water) for 14 days had decreasing antioxidant enzyme activities, evidenced by elevated ROS & RONS levels and histopathological damage via enhancement of inflammatory responses.

Immune system related outcomes

Summary based on Health Canada 2010 report: No animal evidence on immunotoxicity was identified.

Current review evidence synthesis: Two low risk-of-bias tier-1 studies were identified [170, 203]. Gutierrez-Salinas et al. [170] assessed the immunotoxicity of fluoride exposure at or below 20 ppm fluoride in drinking water; however, the observed changes (decreased metabolic activity or increase in apoptotic markers in macrophages) occurred only at higher concentrations (i.e., 50 mg/L). Li et al. [203] also observed immunotoxicity of fluoride exposure changes at 11.25 ppm F and above, as well as histopathological changes of the spleen (an unclear junction between the splenic cortex and medulla, and irregularly shaped cells).

Two additional tier-2 studies were identified [174, 302] . Wang et al. 2019 [302], reported that serum cytokine contents (IL-1β, IL-2, IL-6, and TNF-α) was significantly decreased in Sprague-Dawley rats exposed to NaF 25 and 50 mg/L for 70 days. Hosokawa et al. 2015 [174] showed a decline in relative weights of spleens, in male BALB/c mice exposed to 1 and 5 ppm for 30 days.

Genotoxicity

Summary based on Health Canada 2010 report: “Inconsistencies in the overall results of the studies on the genotoxicity/mutagenicity potential of fluoride do not allow for firm conclusions to be made regarding the genotoxic potential of fluoride although the balance of evidence for genotoxicity of fluoride does not support the view that fluoride is genotoxic in humans.”

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Current review evidence synthesis: One low risk-of-bias tier-1 study [257] was identified to assess the genotoxicity of fluoride exposure at or below 20 ppm fluoride in drinking water. It showed that increase in the percentage of aberrant metaphases and chromatid breaks was more salient in animals treated with 15 mg/L fluoride, than higher doses. Another tier-2 study [256] observed significant increase in percentage of dead cells in bone marrow and in percentage of aberrant cells (cells with chromatid breaks) and chromatid breaks, in male Swiss-albino mice exposed to NaF 15 mg/L for 30 days.

Intestinal outcomes

Summary based on Health Canada 2010 report: No animal evidence on intestinal outcomes was identified.

The current review evidence synthesis: No tier-1 or tier-2 studies were identified to assess the intestinal toxicity in animals exposed to fluoride at or below 20 ppm in drinking water.

Trial Ex. 131.1074

Supplementary Material 5. Excluded animal studies

This supplement provides a list of animal studies identified but considered ineligible for the systematic review, with reasons provided for exclusion at level 1 (title and abstract screening) and level 2 (full text examination). Reasons for exclusion of specific studies are provided.

Table 3: Animal studies excluded at levels 1 and 2 by exclusion reason/group

Level	Exclusion group	Reason for exclusion	# of studies
L1	Ineligible	One or more exclusion criteria	1,628
L2	Language	Non-English publication	76
	Duplicate	Included in NTP 2019	7
	Unavailable full-text	No pdf available	37
	Irrelevant outcome	Outcome out of scope	8
	Irrelevant population	Human subjects	5
		In-vitro models (e.g., mammalian cells/ tissues, bacterial cells, plant cells)	3
	Irrelevant publication type	Non-systematic reviews	11
		Commentary/communication/editorial/letter/ conference abstract/poster/presentation	16
	Other exclusion reasons	Including route of exposure other than drinking water, mixture exposure, non-mammalian species	43

Trial Ex. 131.1075

Excluded animal studies (with reasons for exclusion)

Level	Bibliography	Reason for Exclusion
L1	*North American Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports.* 2019. 10:23	One or more exclusion criteria
L1	Klein, E.,Ciobanu, M.,Klein, J.,Machi, V.,Leborgne, C.,Vandamme, T.,Frisch, B.,Pons, F.,Kichler, A.,Zuber, G.,Lebeau, L.. "HFP" fluorinated cationic lipids for enhanced lipoplex stability and gene delivery. *Bioconjug Chem.* 2010. 21:360-71	One or more exclusion criteria
L1	McInnes, S. J.,Michl, T. D.,Delalat, B.,Al-Bataineh, S. A.,Coad, B. R.,Vasilev, K.,Griesser, H. J.,Voelcker, N. H.. "Thunderstruck": Plasma-Polymer-Coated Porous Silicon Microparticles As a Controlled Drug Delivery System. *ACS Appl Mater Interfaces.* 2016. 8:4467-76	One or more exclusion criteria
L1	Sinha, S.,Vorse, K. S.,Kariya, P. B.,Mallikarjuna, R.. 'Pitted' to 'pleasing' in 20 min. *BMJ Case Reports.* 2015. #volume#:#pages#	One or more exclusion criteria
L1	Fernandez-Maza, L.,Corral, A.,Becerro, A.,Gonzalez, D.,Parrado, A.,Balcerzyk, M.,Ocana, M.. (18)F-fluorination of BaGdF5 nanoparticles for multimodal imaging and PET/CT biodistribution in mouse. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S166-S168	One or more exclusion criteria
L1	Bouchlaka, M.,Gordon, J.,Ludwig, K.,Niles, D.,Bednarz, B.,Fain, S.,Capitini, C.. (19)F-MRI for tracking NK Cells after adoptive transfer. *Journal of Immunology.*	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	Conference: 101st Annual Meeting of the American Association of Immunologist, IMMUNOLOGY. 2014. 192:#pages#	
L1	Chopra, A.. (99m)Tc-glutamate peptide 3-aminoethyl estradiol. *Molecular Imaging and Contrast Agent Database (MICAD).* 2004. #volume#:#pages#	One or more exclusion criteria
L1	Bohmer, V.,Van Der Born, D.,Szymanski, W.,Antunes, I.,Klopstra, M.,Samplonius, D.,Sijbesma, J.,Helfrich, W.,Visser, T.,Feringa, B.,Elsinga, P.. 18 F-labelled click based PSMA-tracer for prostate cancer imaging. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S94-S95	One or more exclusion criteria
L1	Fernandez-Maza, L.,Rivera-Marrero, S.,Balcerzyk, M.,Fernandez-Gomez, I.,Parrado-Gallego, A.,Sablon-Carrazana, M.,Perez-Perera, R.,Diaz-Garcia, O.,Perera-Pintado, A.,Prats-Capote, A.,Rodriguez-Tanty, C.. 18F Labeling of a new naphthalene derivative as potential alzheimer disease PET imaging agent. Synthesis and preclinical studies. *European Journal of Nuclear Medicine and Molecular Imaging.* 2015. 1):S282	One or more exclusion criteria
L1	Sviripa, V. M.,Zhang, W.,Balia, A. G.,Tsodikov, O. V.,Nickell, J. R.,Gizard, F.,Yu, T.,Lee, E. Y.,Dwoskin, L. P.,Liu, C.,Watt, D. S.. 2',6'-Dihalostyrylanilines, pyridines, and pyrimidines for the inhibition of the catalytic subunit of methionine S-adenosyltransferase-2. *J Med Chem.* 2014. 57:6083-91	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
L1	Inkster, J.,Lin, K. S.,Ait-Mohand, S.,Gosselin, S.,Benard, F.,Guerin, B.,Pourghiasian, M.,Ruth, T.,Schaffer, P.,Storr, T.. 2-Fluoropyridine prosthetic compounds for the 18F labeling of bombesin analogues. *Bioorganic & Medicinal Chemistry Letters.* 2013. 23:3920-6	One or more exclusion criteria
L1	Connett, P.. 3rd Citizens Conference of the Fluoride Action Network. *Fluoride.* 2008. 41:175	One or more exclusion criteria
L1	Suzuki, M.,Everett, E. T.,Whitford, G. M.,Bartlett, J. D.. 4-phenylbutyrate Mitigates Fluoride-Induced Cytotoxicity in ALC Cells. *Front Physiol.* 2017. 8:302	One or more exclusion criteria
L1	Mitra, R.,Goddard, R.,Pörschke, K. R.. 9,9-Difluorobispidine Analogues of Cisplatin, Carboplatin, and Oxaliplatin. *Inorg Chem.* 2017. 56:6712-6724	One or more exclusion criteria
L1	Ebenhan, T.,Wagener, J.,Suthiram, J.,Marjanovic, P. B.,Sathekge, M. M.,Zeevaart, J. R.. ⁶⁸Ga-PSMA-11: An one-year performance experience on a singlevial kit-type preparation of a potent PETradiodiagnostic agent for prostate cancer imaging. *Molecular Imaging and Biology.* 2016. 18 (2 Supplement):S1173	One or more exclusion criteria
L1	Perrin, D. M.. [(18)F]-Organotrifluoroborates as Radioprosthetic Groups for PET Imaging: From Design Principles to Preclinical Applications. *Acc Chem Res.* 2016. 49:1333-43	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
L1	Tibrewala, R.,Bahroos, E.,Mehrebian, H.,Foreman, S. C.,Link, T. M.,Pedoia, V.,Majumdar, S.. [18F]-sodium fluoride PET-MR imaging reveals bone-cartilage interactions in hip osteoarthritis. *Osteoarthritis and Cartilage.* 2019. 27 (Supplement 1):S145-S147	One or more exclusion criteria
L1	Frederic, D.,Bertrand, K.,Annelaure, D.,Camp Nadia, V.,Michael, K.,Bertrand, T.,Raphael, B.. [¹⁸F]DPA-716 as a candidate for imaging the TSPO 18 kDa with PET: Radiosynthesis and comparative evaluation ([¹¹C]DPA-713 / [¹⁸F]DPA-714) in a rat model of neuroinflammation. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2011. 1):S275	One or more exclusion criteria
L1	Riondato, M.,Pastorino, S.,Giovannini, E.,Ferrando, O.,Lazzeri, P.,Duce, V.,Ciarmiello, A.. [¹⁸F]FET production with a modified gallium-68 automated synthesizer in a Radiopharmacy without cyclotron facility. *European Journal of Nuclear Medicine and Molecular Imaging.* 2019. 46 (1 Supplement 1):S723	One or more exclusion criteria
L1	Xiong, L.,Shen, B.,Gambhir, S. S.,Chin, F. T.,Rao, J.. [¹⁸F]YF<inf>3</inf> nanoprobes: Novel 18F-labeled imaging agents for tumor targeting. *Molecular Imaging and Biology.* 2012. 1):S168	One or more exclusion criteria
L1	Johanna, R.,Jori, J.,Cesare, F.,Anniina, P.,Juha, R.,Merja, H.,Olof, S.. [C] Novel [F-18] S1P3-receptor tracer for preclinical PET imaging in Alzheimer's	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	disease. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2011. 1):S455	
L1	Palczewska-Komsa, M.. [Comparison of fluoride concentrations in human, dog, fox and raccoon dog bones from northwestern Poland]. *Pomeranian J Life Sci.* 2015. 61:319-28	One or more exclusion criteria
L1	Machoy-Mokrzyńska, A.,Machoy, Z.. [Current trends in fluorine research]. *Ann Acad Med Stetin.* 2006. 52 Suppl 1:73-7	One or more exclusion criteria
L1	Montero, M.,Rojas-Sanchez, F.,Socorro, M.,Torres, J.,Acevedo, A. M.. [Dental caries and fluorosis in children consuming water with different fluoride concentrations in Maiquetia, Vargas State, Venezuela]. *Invest Clin.* 2007. 48:5-19	One or more exclusion criteria
L1	Golubkina, N. A.,Burtseva, T. I.,Gatsenko, AIu. [Drinking water quality indices in the Orenburg Region]. *Gig Sanit.* 2011. #volume#:70-4	One or more exclusion criteria
L1	Yun, Z. J.,Chen, P. Z.,Bian, J. C.,Wang, Y. T.,Gao, J.,Ma, A. H.,Liu, Y.,Li, H. X.. [Epidemiological investigation on endemic fluorosis along the Yellow River alluvial plain of Shandong province]. *Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology.* 2010. 31:1280-3	One or more exclusion criteria
L1	Varenne, B.,Fournet, F.,Cadot, E.,Msellati, P.,Ouedraogo, H. Z.,Meyer, P. E.,Cornu, J. F.,Salem, G.,Petersen, P. E.. [Family environment and dental	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	health disparities among urban children in Burkina Faso]. *Rev Epidemiol Sante Publique.* 2011. 59:385-92	
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L1	Tago, T.,Toyohara, J.,Fujimaki, R.,Hirano, K.,Iwai, K.,Ishibashi, K.,Tanaka, H.. A simple SPE purification method for ¹⁸F-radiolabeling: Proof-of-concept study in stilbene amyloid-beta ligands with a neopentyl labeling group. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S163-S164	One or more exclusion criteria
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L1	Goulding, J. M. R.,Finch, T. M.. Acrylates tooth and nail: Coexistent allergic contact dermatitis to acrylates present in desensitizing dental swabs and artificial fingernails. *British Journal of Dermatology.* 2010. 1):87-88	One or more exclusion criteria
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L1	Lisova, K.,Wang, J.,Rios, A.,Van Dam, R. M.. Adaptation and optimization of [¹⁸F] Florbetaben ([¹⁸F]FBB) radiosynthesis to a	One or more exclusion criteria

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L1	Kisely, S.,Quek, L. H.,Pais, J.,Lalloo, R.,Johnson, N. W.,Lawrence, D.. Advanced dental disease in people with severe mental illness: systematic review and meta-analysis. *Br J Psychiatry.* 2011. 199:187-93	One or more exclusion criteria

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L1	Levine, R.. Advancing the scientific basis of oral health education. *Community Dent Health.* 2015. 32:66-7	One or more exclusion criteria
L1	Babini, M. S.,Bionda, C. L.,Salas, N. E.,Martino, A. L.. Adverse effect of agroecosystem pond water on biological endpoints of common toad (Rhinella arenarum) tadpoles. *Environmental Monitoring and Assessment.* 2016. 188 (8) (no pagination):#pages#	One or more exclusion criteria
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L1	Arulkumar, M.,Vijayan, R.,Penislusshiyan, S.,Sathishkumar, P.,Angayarkanni, J.,Palvannan, T.. Alteration of paraoxonase, arylesterase and lactonase activities in people around fluoride endemic area of Tamil Nadu, India. *Clinica Chimica Acta.* 2017. 471:206-215	One or more exclusion criteria
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L1	Frisardi, V.,Solfrizzi, V.,Capurso, C.,Kehoe, P. G.,Imbimbo, B. P.,Santamato, A.,Dellegrazie, F.,Seripa, D.,Pilotto, A.,Capurso, A.,Panza, F.. Aluminum in the diet and Alzheimer's disease: from current epidemiology to possible disease-modifying treatment. *J Alzheimers Dis.* 2010. 20:17-30	One or more exclusion criteria
L1	Shaw, C. A.,Seneff, S.,Kette, S. D.,Tomljenovic, L.,Oller, J. W.,Davidson, R. M.. Aluminum-induced entropy in biological systems: Implications for neurological disease. *Journal of Toxicology.* 2014. 2014 (no pagination):#pages#	One or more exclusion criteria
L1	Seo, E. J.,Lee, M. Y.. Amelioration of hydrofluoric acid-induced DNA damage by phytochemicals. *Toxicology and Environmental Health Sciences.* 2013. 5:201-206	One or more exclusion criteria
L1	Kushi, L. H.,Byers, T.,Doyle, C.,Bandera, E. V.,McCullough, M.,Gansler, T.,Andrews, K. S.,Thun, M. J.,Ainsworth, B.,Ballard-Barbash, R.,Bloch, A. F.,Chan, J. M.,Coates, R. J.,Demark-Wahnefried, W.,Freudenheim, J.,Gann, P.,Giovannucci, E.,Hartman, T.,Kolonel, L.,Lichtenstein, A. H.,Martinez, M. E.,McTiernan, A.,Morra, M.,Schatzkin, A.,Slattery, M.,Smith-Warner, S.,Wylie-Rosett, J.,Zheng, W.,Ades, T.,Cokkinides, V.,Samuels, A.,Ringer, D. P.,Smith,	One or more exclusion criteria

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L1	Fewtrell, L.,Smith, S.,Kay, D.,Bartram, J.. An attempt to estimate the global burden of disease due to fluoride in drinking water. *J Water Health.* 2006. 4:533-42	One or more exclusion criteria
L1	Jiang, G.,Pichaandi, J.,Johnson, N. J.,Burke, R. D.,van Veggel, F. C.. An effective polymer cross-linking strategy to obtain stable dispersions of upconverting NaYF4 nanoparticles in buffers and biological growth media for biolabeling applications. *Langmuir.* 2012. 28:3239-47	One or more exclusion criteria
L1	Kao, C. H.,Hsu, W. L.,Kao, P. F.,Lan, W. C.,Xie, H. L.,Lin, M. C.,Chao, H. Y.. An efficient and aseptic preparation of "sodium fluoride ((18)F) injection" in a GMP compliant facility. *Ann Nucl Med.* 2010. 24:149-55	One or more exclusion criteria
L1	Erickson, J. D.. An epidemiologic enterprise: From fluoride to folate. *Birth Defects Research Part A - Clinical and Molecular Teratology.* 2012. 94 (5):292	One or more exclusion criteria

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L1	Sankannavar, R.,Chaudhari, S.. An imperative approach for fluorosis mitigation: Amending aqueous calcium to suppress hydroxyapatite dissolution in defluoridation. *Journal of Environmental Management.* 2019. 245:230-237	One or more exclusion criteria
L1	Olley, R. C.,Pilecki, P.,Hughes, N.,Jeffery, P.,Austin, R. S.,Moazzez, R.,Bartlett, D.. An in situ study investigating dentine tubule occlusion of dentifrices following acid challenge. *J Dent.* 2012. 40:585-93	One or more exclusion criteria
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L1	Ye, Y.,Wang, W.,Huo, L. L.,Liu, K. K.,Liu, Y.,Sun, J.,Li, S. P.,Gao, Y. H.. An investigation of the source of fluoride in the endemic fluorosis areas of Pingxiang city, Jiangxi province in 2011. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:67-70	One or more exclusion criteria
L1	Liu, Y.,Guo, R.,Huang, J.,Wang, X.,Yang, F.,Sun, G.. An survey of endemic fluorosis in Jining City, Shandong Province. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:174-177	One or more exclusion criteria
L1	Honkanen, I.,Hock, L.,Bettendorf, B.,Fiordellisi, W.. An unlikely source of periostitis. *Journal of General Internal Medicine.* 2018. 33 (2 Supplement 1):464	One or more exclusion criteria
L1	Susan, J.,Sebastian, S.. An unusual cause of back pain in South India: Case report. *Turkish Journal of Gastroenterology.* 2019. 30 (Supplement 3):S190-S191	One or more exclusion criteria
L1	Dai, H. X.,Zeng, P.,Wang, K. Y.,Zhang, X. G.,Ma, Z. J.,Zhou, Y. G.,Fan, Z. X.,Guo, S. H.. Analysis of a survey results of patients with suspected high iodine goiter in Liuji Town Fuping County of Shaanxi Province. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:408-411	One or more exclusion criteria

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L1	Chen, J.,Xiao, B. Z.,Yan, W.,Zhou, Q. R.,Zhang, J.,Wang, Z. H.,Zhao, J.,Guo, X. L.,Luo, X. J.. Analysis of environmental fluoride of the coal-burning endemic fluorosis areas in Chongqing. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:541-544	One or more exclusion criteria

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L1	Jumba, I. O.,Kisia, S. M.,Kock, R.. Animal health problems attributed to environmental contamination in Lake Nakuru National Park, Kenya: A case study on heavy metal poisoning in the waterbuck Kobus ellipsiprymnus defassa (Ruppel 1835). *Archives of Environmental Contamination and Toxicology.* 2007. 52:270-281	One or more exclusion criteria
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L1	Vasant, R. A.,Khajuria, M. C.,Narasimhacharya, A. V.. Antioxidant and ACE enhancing potential of Pankajakasthuri in fluoride toxicity: an in vitro study on mammalian lungs. *Toxicology & Industrial Health.* 2011. 27:793-801	One or more exclusion criteria
L1	Rocha-Amador, D. O.,Calderon, J.,Carrizales, L.,Costilla-Salazar, R.,Perez-Maldonado, I. N.. Apoptosis of peripheral blood mononuclear cells in children exposed to arsenic and fluoride. *Environmental Toxicology & Pharmacology.* 2011. 32:399-405	One or more exclusion criteria
L1	Wang, J. H.,Feng, X. W.,Zheng, Z. X.,Liu, W.,Li, Z. R.,Gao, R.,Wang, S. Q.,Wang, E. L.,Kan, Z. Y.,Zhao, W. G.,Guo, J. Q.. Application of global positioning systems and geographic information systems in drinking water defluoridation project in Liaoning province. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:544-546	One or more exclusion criteria
L1	Shan, L. H.,Cui, Z. Q.,Shen, Q. H.,Gao, Q.,Qiu, Z. X.. Application of light-cure resin-modified glass ionomer cement in orthodontic practice. *Journal of Clinical Rehabilitative Tissue Engineering Research.* 2008. 12:1149-1152	One or more exclusion criteria

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L1	Lazari, M.,Sergeev, M.,Morgia, F.,Van Dam, R.. Application of titanium dioxide in catalytic radiofluorination in aqueous media. *Molecular Imaging and Biology. Conference.* 2014. 17:#pages#	One or more exclusion criteria
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L1	Mor, S.,Singh, S.,Yadav, P.,Rani, V.,Rani, P.,Sheoran, M.,Singh, G.,Ravindra, K.. Appraisal of salinity and fluoride in a semi-arid region of India using statistical and multivariate techniques. *Environ Geochem Health.* 2009. 31:643-55	One or more exclusion criteria

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L1	Anjomshoaa, I.,Briseño-Ruiz, J.,Deeley, K.,Poletta, F. A.,Mereb, J. C.,Leite, A. L.,Barreta, P. A.,Silva, T. L.,Dizak, P.,Ruff, T.,Patir, A.,Koruyucu, M.,Abbasoğlu, Z.,Casado, P. L.,Brown, A.,Zaky, S. H.,Bayram, M.,Küchler, E. C.,Cooper, M. E.,Liu, K.,Marazita, M. L.,Tanboğa, İ,Granjeiro, J. M.,Seymen, F.,Castilla, E. E.,Orioli, I. M.,Sfeir, C.,Owyang, H.,Buzalaf, M. A.,Vieira, A. R.. Aquaporin 5 Interacts with Fluoride and Possibly Protects against Caries. *PLoS One.* 2015. 10:e0143068	One or more exclusion criteria
L1	Pandith, M.,Malpe, D. B.,Rao, A. D.,Rao, P. N.. Aquifer wise seasonal variations and spatial distribution of major ions with focus on fluoride contamination-Pandharkawada block, Yavatmal district, Maharashtra, India. *Environmental Monitoring and Assessment.* 2016. 188:1-20	One or more exclusion criteria
L1	Hu, Q.,Strynar, M. J.,DeWitt, J. C.. Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA?. *Journal of Immunotoxicology.* 2010. 7:344-9	One or more exclusion criteria
L1	Peckham, S.,Lowery, D.,Spencer, S.. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational	One or more exclusion criteria

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L1	Farooqi, A.,Sultana, J.,Masood, N.. Arsenic and fluoride co-contamination in shallow aquifers from agricultural suburbs and an industrial area of Punjab, Pakistan: Spatial trends, sources and human health implications. *Toxicol Ind Health.* 2017. 33:655-672	One or more exclusion criteria
L1	Qurat ul, Ain,Farooqi, A.,Sultana, J.,Masood, N.. Arsenic and fluoride co-contamination in shallow aquifers from agricultural suburbs and an industrial area of Punjab, Pakistan: Spatial trends, sources and human health implications. *Toxicology & Industrial Health.* 2017. 33:655-672	One or more exclusion criteria
L1	Estrada-Capetillo, B. L.,Ortiz-Pérez, M. D.,Salgado-Bustamante, M.,Calderón-Aranda, E.,Rodríguez-Pinal, C. J.,Reynaga-Hernández, E.,Corral-Fernández, N. E.,González-Amaro, R.,Portales-Pérez, D. P.. Arsenic and fluoride co-exposure affects the expression of apoptotic and inflammatory genes and proteins in mononuclear cells from children. *Mutat Res Genet Toxicol Environ Mutagen.* 2014. 761:27-34	One or more exclusion criteria

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L1	Wang, S. X.,Cheng, X. T.,Li, J.,Sang, Z. P.,Zhang, X. D.,Han, L. L.,Qiao, X. Y.,Wu, Z. M.,Wang, Z. H.. Arsenic and fluoride expose in drinking water: Children's IQ and growth in Shanyin Country, Shanxi Province, China. *Environmental Health Perspectives.* 2007. 115:643-647	One or more exclusion criteria
L1	Chouhan, S.,Flora, S. J.. Arsenic and fluoride: two major ground water pollutants. *Indian Journal of Experimental Biology.* 2010. 48:666-78	One or more exclusion criteria
L1	Peterson, E.,Shapiro, H.,Li, Y.,Minnery, J. G.,Copes, R.. Arsenic from community water fluoridation: quantifying the effect. *J Water Health.* 2016. 14:236-42	One or more exclusion criteria
L1	Villanueva, C. M.,Kogevinas, M.,Cordier, S.,Templeton, M. R.,Vermeulen, R.,Nuckols, J. R.,Nieuwenhuijsen, M. J.,Levallois, P.. Assessing exposure and health consequences of chemicals in drinking water: Current state of knowledge and research needs. *Environmental Health Perspectives.* 2014. 122:213-221	One or more exclusion criteria
L1	Augustsson, A.,Berger, T.. Assessing the risk of an excess fluoride intake among Swedish children in households with private wells - Expanding static	One or more exclusion criteria

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L1	Kalshetty, B. M.,Gaonkar, S. M.,Gani, R. S.,Kalashetti, M. B.. Assessment and toxicity of fluoride from ground water sources in and around Bagalkot district, Karnataka, India. *International Research Journal of Pharmacy.* 2013. 4:246-249	One or more exclusion criteria
L1	Pollo, F. E.,Grenat, P. R.,Otero, M. A.,Salas, N. E.,Martino, A. L.. Assessment in situ of genotoxicity in tadpoles and adults of frog Hypsiboas cordobae (Barrio 1965) inhabiting aquatic ecosystems associated to fluorite mine. *Ecotoxicol Environ Saf.* 2016. 133:466-74	One or more exclusion criteria
L1	Valeeva, E. R.,Ismagilova, G. A.,Stepanova, N. V.,Serazetdinova, F. I.,Saifullin, R. R.,Iliasova, A. R.. Assessment of adolescents' exposure to non-carcinogenic risk associated with drinking water. *Journal of Pharmacy Research.* 2017. 11:1209-1213	One or more exclusion criteria
L1	Sarinana-Ruiz, Y. A.,Vazquez-Arenas, J.,Sosa-Rodriguez, F. S.,Labastida, I.,Armienta, M. A.,Aragon-Pina, A.,Escobedo-Bretado, M. A.,Gonzalez-Valdez, L. S.,Ponce-Pena, P.,Ramirez-Aldaba, H.,Lara, R. H.. Assessment of arsenic and fluorine in surface soil to determine environmental and health risk factors in the Comarca Lagunera, Mexico. *Chemosphere.* 2017. 178:391-401	One or more exclusion criteria

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L1	Arshad, N.,Imran, S.. Assessment of arsenic, fluoride, bacteria, and other contaminants in drinking water sources for rural communities of Kasur and other districts in Punjab, Pakistan. *Environ Sci Pollut Res Int.* 2017. 24:2449-2463	One or more exclusion criteria
L1	Wang, T. J.,An, J.,Chen, X. H.,Deng, Q. D.,Yang, L.. Assessment of Cuscuta chinensis seeds′ effect on melanogenesis: comparison of water and ethanol fractions in vitro and in vivo. *J Ethnopharmacol.* 2014. 154:240-8	One or more exclusion criteria
L1	Malinowska, E.,Inkielewicz, I.,Czarnowski, W.,Szefer, P.. Assessment of fluoride concentration and daily intake by human from tea and herbal infusions. *Food Chem Toxicol.* 2008. 46:1055-61	One or more exclusion criteria
L1	Bhat, N.,Jain, S.,Asawa, K.,Tak, M.,Shinde, K.,Singh, A.,Gandhi, N.,Gupta, V. V.. Assessment of Fluoride Concentration of Soil and Vegetables in Vicinity of Zinc Smelter, Debari, Udaipur, Rajasthan. *J Clin Diagn Res.* 2015. 9:Zc63-6	One or more exclusion criteria

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L1	Vincent, J.,Balakumar, P.. Assessment of fluoride concentrations of groundwater in Tiruchendur, Thoothukudi district, Tamilnadu by spadns method. *International Journal of ChemTech Research.* 2014. 6:4807-4809	One or more exclusion criteria
L1	Dutta, J.. Assessment of fluoride, arsenic and other heavy metals in the ground water of tea gardens belt of Sonitpur district, Assam, India. *International Journal of ChemTech Research.* 2016. 9:71-79	One or more exclusion criteria
L1	de Souza, C. F.,Lima, J. F., Jr.,Adriano, M. S.,de Carvalho, F. G.,Forte, F. D.,de Farias Oliveira, R.,Silva, A. P.,Sampaio, F. C.. Assessment of groundwater quality in a region of endemic fluorosis in the northeast of Brazil. *Environmental Monitoring & Assessment.* 2013. 185:4735-43	One or more exclusion criteria
L1	Cooray, T.,Wei, Y.,Zhong, H.,Zheng, L.,Weragoda, S. K.,Weerasooriya, A. R.. Assessment of Groundwater Quality in CKDu Affected Areas of Sri Lanka: Implications for Drinking Water Treatment. *Int J Environ Res Public Health.* 2019. 16:#pages#	One or more exclusion criteria
L1	Ranjan, S.,Yasmin, S.. Assessment of groundwater quality in Gaya region with respect to fluoride. *Journal of Ecophysiology and Occupational Health.* 2012. 12:21-25	One or more exclusion criteria
L1	Tunakova, J.,Galimova, A.,Fajzullin, R.,Valiev, V.. Assessment of health risks of the child population in the consumption of drinking water, taking into account	One or more exclusion criteria

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L1	Meng, F.,Zhao, R.,Liu, P.,Liu, L.,Liu, S.. Assessment of iodine status in children, adults, pregnant women and lactating women in iodine-replete areas of china. *PLoS ONE.* 2013. 8 (11) (no pagination):#pages#	One or more exclusion criteria
L1	Francisca, F. M.,Carro Perez, M. E.. Assessment of natural arsenic in groundwater in Cordoba Province, Argentina. *Environ Geochem Health.* 2009. 31:673-82	One or more exclusion criteria
L1	Corcia, P.,Vercouillie, J.,Tauber, C.,Praline, J.,Nicolas, G.,Venel, Y.,Beaulieu, J. L.,Aesch, C.,Roussel, C.,Kassiou, M.,Guilloteau, D.,Ribeiro, M.. Assessment of neuroinflammation in als with 18F-DPA-714 PET. *Amyotrophic Lateral Sclerosis.* 2012. 1):54-55	One or more exclusion criteria
L1	Kundu, M. C.,Mandal, B.. Assessment of potential hazards of fluoride contamination in drinking groundwater of an intensively cultivated district in West Bengal, India. *Environmental Monitoring and Assessment.* 2009. 152:97-103	One or more exclusion criteria
L1	Bhattacharya, P.,Samal, A. C.,Banerjee, S.,Pyne, J.,Santra, S. C.. Assessment of potential health risk of fluoride consumption through rice, pulses, and vegetables in addition to consumption of fluoride-contaminated drinking water of West Bengal, India. *Environ Sci Pollut Res Int.* 2017. 24:20300-20314	One or more exclusion criteria

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L1	Li, Z.,Yang, K.,Xie, C.,Yang, Q.,Lei, X.,Wang, H.. Assessment of potential health risk of major contaminants of groundwater in a densely populated agricultural area. *Environ Geochem Health.* 2019. #volume#:#pages#	One or more exclusion criteria
L1	Rawlani, S.,Rawlani, S.,Rawlani, S.. Assessment of Skeletal and Non-skeletal Fluorosis in Endemic Fluoridated Areas of Vidharbha Region, India: A Survey. *Indian Journal of Community Medicine.* 2010. 35:298-301	One or more exclusion criteria
L1	Meena, C.,Dwivedi, S.,Rathore, S.,Gonmei, Z.,Toteja, G. S.,Bala, K.,Mohanty, S. S.. Assessment of skeletal fluorosis among children in two blocks of rural area, Jaipur District, Rajasthan, India. *Asian Journal of Pharmaceutical and Clinical Research.* 2017. 10:322-325	One or more exclusion criteria
L1	Ye, Q.,Zhou, X.. Assessment of Soil Fluorine Pollution in Jinhua Fluorite Ore Areas. [Chinese]. *Huan jing ke xue= Huanjing kexue / [bian ji, Zhongguo ke xue yuan huan jing ke xue wei yuan hui "Huan jing ke xue" bian ji wei yuan hui.].* 2015. 36:2648-2654	One or more exclusion criteria
L1	Radić, S.,Gregorović, G.,Stipaničev, D.,Cvjetko, P.,Srut, M.,Vujčić, V.,Oreščanin, V.,Vinko Klobučar, G. I.. Assessment of surface water in the vicinity of fertilizer factory using fish and plants. *Ecotoxicol Environ Saf.* 2013. 96:32-40	One or more exclusion criteria
L1	West, N. X.,Seong, J.,Hellin, N.,Macdonald, E. L.,Jones, S. B.,Creeth, J. E.. Assessment of tubule occlusion properties of an experimental stannous	One or more exclusion criteria

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L1	Viswanathan, G.,Gopalakrishnan, S.,Siva Ilango, S.. Assessment of water contribution on total fluoride intake of various age groups of people in fluoride endemic and non-endemic areas of Dindigul District, Tamil Nadu, South India. *Water Research.* 2010. 44:6186-6200	One or more exclusion criteria
L1	Gehani, C. P.,Pollick, H.,Stevenson, R. A.. Association between Maternal Fluoride Exposure and Child IQ [8]. *JAMA Pediatrics.* 2020. 174:215-216	One or more exclusion criteria
L1	Green, R.,Lanphear, B.,Hornung, R.,Flora, D.,Martinez-Mier, E. A.,Neufeld, R.,Ayotte, P.,Muckle, G.,Till, C.. Association between Maternal Fluoride Exposure during Pregnancy and IQ Scores in Offspring in Canada. *JAMA Pediatrics.* 2019. 173:940-948	One or more exclusion criteria
L1	Yang, D.,Liu, Y.,Chu, Y.,Yang, Q.,Jiang, W.,Chen, F.,Li, D.,Qin, M.,Sun, D.,Yang, Y.,Gao, Y.. Association between vitamin D receptor gene FokI polymorphism and skeletal fluorosis of the brick-tea type fluorosis: a cross sectional, case control study. *BMJ Open.* 2016. 6:e011980	One or more exclusion criteria
L1	Patel, P. P.,Patel, P. A.,Zulf, M. M.,Yagnik, B.,Kajale, N.,Mandlik, R.,Khadilkar, V.,Chiplonkar, S. A.,Phanse, S.,Patwardhan, V.,Joshi, P.,Patel, A.,Khadilkar, A. V.. Association of dental and skeletal fluorosis with calcium intake and	One or more exclusion criteria

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L1	Choi, A. L.,Zhang, Y.,Sun, G.,Bellinger, D. C.,Wang, K.,Yang, X. J.,Li, J. S.,Zheng, Q.,Fu, Y.,Grandjean, P.. Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot study. *Neurotoxicol Teratol.* 2015. 47:96-101	One or more exclusion criteria
L1	Asawa, K.,Singh, A.,Bhat, N.,Tak, M.,Shinde, K.,Jain, S.. Association of Temporomandibular Joint Signs & Symptoms with Dental Fluorosis & Skeletal Manifestations in Endemic Fluoride Areas of Dungarpur District, Rajasthan, India. *Journal of Clinical and Diagnostic Research JCDR.* 2015. 9:ZC18-21	One or more exclusion criteria
L1	Chafe, R.,Aslanov, R.,Sarkar, A.,Gregory, P.,Comeau, A.,Newhook, L. A.. Association of type 1 diabetes and concentrations of drinking water components in Newfoundland and Labrador, Canada. *BMJ Open Diabetes Research and Care.* 2018. 6 (1) (no pagination):#pages#	One or more exclusion criteria
L1	Riddell, J. K.,Malin, A. J.,Flora, D.,McCague, H.,Till, C.. Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in North American youth. *Environ Int.* 2019. 133:105190	One or more exclusion criteria
L1	Furukawa, S.,Hagiwara, Y.,Taguchi, C.,Turumoto, A.,Kobayashi, S.. Associations between oral health behavior and anxiety about water fluoridation	One or more exclusion criteria

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	and motivation to establish water fluoridation in Japanese residents. *Journal of Oral Science.* 2011. 53:313-9	
L1	Oweis, R.,Levy, S.,Warren, J.,Gilmore, J. E.,Burns, T.,Saha, P.,Janz, K.,Torner, J.,Letuchy, E.,Broffitt, B.. Associations of fluoride intake with adolescents' pQCT-derived bone outcome measures at age 17. *Journal of Bone and Mineral Research. Conference.* 2015. 30:#pages#	One or more exclusion criteria
L1	Levy, S. M.,Eichenberger-Gilmore, J.,Warren, J. J.,Letuchy, E.,Broffitt, B.,Marshall, T. A.,Burns, T.,Willing, M.,Janz, K.,Torner, J. C.. Associations of fluoride intake with children's bone measures at age 11. *Community Dent Oral Epidemiol.* 2009. 37:416-26	One or more exclusion criteria
L1	Spittle, B.. Authority and reasoning in science. *Fluoride.* 2014. 47:94-97	One or more exclusion criteria
L1	Teotia, S. P. S.,Teotia, M.. Authors's response. *Indian Journal of Medical Research.* 2008. 128:674-676	One or more exclusion criteria
L1	Hader, S.. Automated GMP compatible synthesis of 3-[18F] Fluoro-5-[(pyridine-2-yl)ethynyl]benzonitrile ([18F] FPEB). *European Journal of Nuclear Medicine and Molecular Imaging.* 2015. 1):S478-S479	One or more exclusion criteria
L1	Anzellotti, A.,Bailey, J.,Ferguson, D.,McFarland, A.,Bochev, P.,Andreev, G.,Awasthi, V.,Brown-Proctor, C.. Automated production and quality testing of	One or more exclusion criteria

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L1	Mossine, A.,Tanzey, S.,Brooks, A.,Henderson, B.,Skaddan, M.,Sanford, M.,Scott, P.. Automated production of high specific activity [¹⁸F]6F-l-DOPA using a TRACERLab FXFN synthesis module. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S225-S226	One or more exclusion criteria
L1	Zhang, Y.,Zhang, L.,Wu, Z.,Yang, J.,Ploessl, K.,Zha, Z.,Fei, L.,Zhu, H.,Zhu, L.,Yang, Z.,Kung, H.. Automated radiosynthesis of (2S,4R)-4-[¹⁸F]fluoroglutamine for clinical application. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S322-S323	One or more exclusion criteria
L1	Collier, T. L.,Yokell, D. L.,Livni, E.,Rice, P. A.,Celen, S.,Serdons, K.,Neelamegam, R.,Bormans, G.,Harris, D.,Walji, A.,Hostetler, E. D.,Bennacef, I.,Vasdev, N.. Automated radiosynthesis of [¹⁸F]MK-6240 and validation for human use. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2017. 60 (Supplement 1):S612	One or more exclusion criteria
L1	Shih, I. H.,Duan, X. D.,Kong, F. L.,Williams, M. D.,Yang, K.,Zhang, Y. H.,Yang, D. J.. Automated synthesis of 18F-fluoropropoxytryptophan for amino acid transporter system imaging. *Biomed Res Int.* 2014. 2014:492545	One or more exclusion criteria

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L1	Noh, M. F. B. M.,Laurens, E.,Jeow, S. Y.,Vedarethinam, R.,Wee, X. J.,Fatholmoein, F. Z. B.,Pek, G.,Ping, H. T. S.,Green, D.,Chiam, V. K.,Boodeea, K.,Doshi, P. R.,Kulasi, A.,Hui, E. T. J.,Weekes, A.,Robins, E.. Automated synthesis of [¹⁸F]NAV4694 using GE TracerLab FX-N Pro in compliance with PIC/S GMP. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S333-S334	One or more exclusion criteria
L1	Bowden, G.,Franke, A.,Pichler, B.,Maurer, A.. Automated synthesis of [¹⁸F]O⁶-[(4-[¹⁸F]fluoro)benzyl]guanine ([¹⁸F]pFBG) via [¹⁸F]-fluorobenzyl alcohol ([¹⁸F]4FBnOH) from an optimized copper mediated radiofluorination (CMRF) of 4-tributyltin-benzyl alcohol. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S329-S331	One or more exclusion criteria
L1	Mitra, A.,Rajesh, C.,Lad, S.,Upadhye, T.,Banerjee, S.,Rajan, R.. Automated synthesis of pharmaceutical grade [¹⁸F]FLT using 5'-O-(Benzoyl)-2,3'-anhydrothymidine Precursor. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2017. 60 (Supplement 1):S616	One or more exclusion criteria
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L1	Souza, M. S.,Diniz, L. F.,Vogt, L.,Carvalho, P. S.,D'Vries, R. F.,Ellena, J.. Avoiding irreversible 5-fluorocytosine hydration: Via supramolecular synthesis of pharmaceutical cocrystals. *New Journal of Chemistry.* 2018. 42:14994-15005	One or more exclusion criteria
L1	Manthra Prathoshni, S. M.,Vishnu Priya, V.,Sohara Parveen, N.. Awareness of dental fluorosis among children - A survey. *Journal of Pharmaceutical Sciences and Research.* 2017. 9:459-461	One or more exclusion criteria
L1	Bansal, R.,Tiwari, S. C.. Back pain in chronic renal failure. *Nephrol Dial Transplant.* 2006. 21:2331-2	One or more exclusion criteria
L1	Grandtnerova, B.,Beratsova, Z.,Ova, M. E.,Erven, J.,Markech, M.,Stefanikova, A.. Balneotherapy and chronic urinary tract infections, a benefit or a danger?. *Nephrology Dialysis Transplantation.* 2014. 3):iii393	One or more exclusion criteria

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L1	Sahin-Onat, S.,Tasoglu, O.,Ozisler, Z.,Demircioglu Guneri, F.,Ozgirgin, N.. Balneotherapy in the treatment of knee osteoarthritis: A controlled study. *Archives of Rheumatology.* 2015. 30:292-297	One or more exclusion criteria
L1	MacGregor, R.. Battle renewed over value of fluoridation. *Cmaj.* 2011. 183:1173	One or more exclusion criteria
L1	Sonne, C.,Lam, S. S.,Kim, K. H.,Rinklebe, J.,Ok, Y. S.. Be cautious applying carbon-fluorine bonds in drug delivery. *Chemosphere.* 2020. 248 (no pagination):#pages#	One or more exclusion criteria
L1	Szoke, D.,Valente, C.,Panteghini, M.. Better blood collection tubes for plasma glucose: Ready for prime time?. *Clinical Chemistry and Laboratory Medicine.* 2014. 52:e87-e89	One or more exclusion criteria
L1	Gilbert, F. J.. Beyond FDG: Getting new PET tracers into practice. *Journal of Medical Imaging and Radiation Oncology.* 2016. 60 (Supplement 1):33	One or more exclusion criteria
L1	Brooks, A.,Burris, S.,Scott, P.. Binding of [¹⁸F]N-Methyl lansoprazole to tau aggregates in post-mortem brain sections from alzheimer's disease and progressive supranuclear palsy patients. *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2017. 58:#pages#	One or more exclusion criteria

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L1	Neale, P. A.,Antony, A.,Bartkow, M. E.,Farré, M. J.,Heitz, A.,Kristiana, I.,Tang, J. Y.,Escher, B. I.. Bioanalytical assessment of the formation of disinfection byproducts in a drinking water treatment plant. *Environ Sci Technol.* 2012. 46:10317-25	One or more exclusion criteria
L1	Athapattu, B. C. L.,Thalgaspitiya, Twlr,Yasaratne, U. L. S.,Vithanage, M.. Biochar-based constructed wetlands to treat reverse osmosis rejected concentrates in chronic kidney disease endemic areas in Sri Lanka. *Environ Geochem Health.* 2017. 39:1397-1407	One or more exclusion criteria
L1	Jaganmohan, P.,Narayana Rao, S. V. L.,Sambasiva Rao, K. R. S.. Biochemical and haematological investigations on fluorosis threaten patients at Nellore district, Andhra Pradesh, India. *World Journal of Medical Sciences.* 2010. 5:54-58	One or more exclusion criteria
L1	Wagner, O.,Thiele, J.,Weinhart, M.,Mazutis, L.,Weitz, D. A.,Huck, W. T.,Haag, R.. Biocompatible fluorinated polyglycerols for droplet microfluidics as an alternative to PEG-based copolymer surfactants. *Lab Chip.* 2016. 16:65-9	One or more exclusion criteria

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L1	Palliyal, S. A.. Biological markers serum and urinary fluoride levels among fertilizer and wood industry workers in Mangalore city, India. *Annals of Oncology.* 2015. 9):ix14	One or more exclusion criteria
L1	Idowu, O. S.,Duckworth, R. M.,Valentine, R. A.,Zohoori, F. V.. Biomarkers for the Assessment of Fluoride Exposure in Children. *Caries Res.* 2020. #volume#:1-10	One or more exclusion criteria
L1	Rango, T.,Vengosh, A.,Jeuland, M.,Whitford, G. M.,Tekle-Haimanot, R.. Biomarkers of chronic fluoride exposure in groundwater in a highly exposed population. *Sci Total Environ.* 2017. 596-597:1-11	One or more exclusion criteria
L1	Zhang, X.,Li, Y.,Sun, X.,Kishen, A.,Deng, X.,Yang, X.,Wang, H.,Cong, C.,Wang, Y.,Wu, M.. Biomimetic remineralization of demineralized enamel with nano-complexes of phosphorylated chitosan and amorphous calcium phosphate. *J Mater Sci Mater Med.* 2014. 25:2619-28	One or more exclusion criteria
L1	Zillohu, A. U.,Abdelaziz, R.,Homaeigohar, S.,Krasnov, I.,Müller, M.,Strunskus, T.,Elbahri, M.. Biomimetic transferable surface for a real time control over wettability and photoerasable writing with water drop lens. *Sci Rep.* 2014. 4:7407	One or more exclusion criteria

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L1	Chen, Y.,Shen, C.,Rashid, S.,Li, S.,Ali, B. A.,Liu, J.. Biopolymer-induced morphology control of brushite for enhanced defluorination of drinking water. *J Colloid Interface Sci.* 2017. 491:207-215	One or more exclusion criteria
L1	Lindner, J. M.,Vogeser, M.,Grimm, S. H.. Biphenyl based stationary phases for improved selectivity in complex steroid assays. *Journal of Pharmaceutical & Biomedical Analysis.* 2017. 142:66-73	One or more exclusion criteria
L1	Waugh, D. T.,Godfrey, M.,Limeback, H.,Potter, W.. Black Tea Source, Production, and Consumption: Assessment of Health Risks of Fluoride Intake in New Zealand. *J Environ Public Health.* 2017. 2017:5120504	One or more exclusion criteria
L1	Spencer, K. F.,Limeback, H.. Blood is thicker than water: Flaws in a National Toxicology Program study. *Medical Hypotheses.* 2018. 121:160-163	One or more exclusion criteria
L1	Mechlenburg, I.,Hermansen, F.,Thillemann, T.,Soballe, K.. Blood perfusion and bone formation before and after minimally invasive periacetabular osteotomy analysed by Positron Emission Tomography combined with Computed Tomography. *International Orthopaedics.* 2013. 37:789-94	One or more exclusion criteria

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L1	Godebo, T. R.,Jeuland, M.,Tekle-Haimanot, R.,Shankar, A.,Alemayehu, B.,Assefa, G.,Whitford, G.,Wolfe, A.. Bone quality in fluoride-exposed populations: A novel application of the ultrasonic method. *Bone Reports.* 2020. 12 (no pagination):#pages#	One or more exclusion criteria
L1	Topuz, O.,Akkaya, N.,Ardic, F.,Sarsan, A.,Cubukcu, D.,Gokgoz, A.. Bone resorption marker and ultrasound measurements in adults residing in an endemic fluorosis area of Turkey. *Fluoride.* 2006. 39:138-144	One or more exclusion criteria
L1	Yildiz, M.,Suslu, H.,Cerci, S.,Ozbek, M.,Cerci, C.. Bone scintigraphy findings in endemic skeletal fluorosis. [Turkish]. *Sendrom.* 2007. 19:83-85	One or more exclusion criteria
L1	Choubisa, S. L.. Bovine calves as ideal bio-indicators for fluoridated drinking water and endemic osteo-dental fluorosis. *Environmental Monitoring & Assessment.* 2014. 186:4493-8	One or more exclusion criteria
L1	Singh, S. T.,Dua, K.,Gupta, D. K.,Randhawa, S. S.,Bansal, B. K.. Bovine fluorosis and its effects on essential minerals, haemogram and biochemical status in the fluoride endemic South-West Punjab of India. *Indian Journal of Animal Sciences.* 2017. 87:718-722	One or more exclusion criteria

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L1	Wei, S.,Lu, Q.,Yang, P.,Chen, P.,Li, S.,La, C.,Jiang, H.,He, D.,Wu, H.,Ma, T.. Brick-tea type fluorosis in monks in Qinghai Province. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:327-330	One or more exclusion criteria
L1	Wang, H.,Teng, G. X.. Brief instruction of the prevention of endemic fluorosis. [Chinese]. *Chinese Journal of Clinical Rehabilitation.* 2006. 10:222-225	One or more exclusion criteria
L1	Chen, W. C.,Ju, C. P.,Wang, J. C.,Hung, C. C.,Chern Lin, J. H.. Brittle and ductile adjustable cement derived from calcium phosphate cement/polyacrylic acid composites. *Dent Mater.* 2008. 24:1616-22	One or more exclusion criteria
L1	. CADTH Rapid Response Reports. *Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects.* 2019. #volume#:#pages#	One or more exclusion criteria
L1	Hopper, K.,Morales, P.,Garcia, A.,Wagner, J.. Camptomelia in a rhesus macaque (Macaca mulatta). *J Am Assoc Lab Anim Sci.* 2010. 49:863-7	One or more exclusion criteria
L1	Suresh, A.,Khairkar, P.,Srujana,. Can high levels of fluoride in body tissues of adolescents impair clinical, psychological, neurocognitive and developmental domains? A qualitative, analytical study from highly fluoride endemic district from south India. *Indian Journal of Psychiatry.* 2020. 62 (7 Supplement 1):S61	One or more exclusion criteria
L1	Frederic, D.,Stephane, L. H.,Marie-Anne, P.,Wadad, S.,Samuel, B.,Nicolas, T.,Heric, V.,Michael, K.. Carbon-11-labelling of a novel, trishomocubane-	One or more exclusion criteria

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L1	Almerich-Silla, J. M.,Montiel-Company, J. M.,Ruiz-Miravet, A.. Caries and dental fluorosis in a western Saharan population of refugee children. *Eur J Oral Sci.* 2008. 116:512-7	One or more exclusion criteria
L1	Jarjoura, K.,Gagnon, G.,Nieberg, L.. Caries risk after interproximal enamel reduction. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2006. 130:26-30	One or more exclusion criteria
L1	Sami, E.,Vichayanrat, T.,Satitvipawee, P.. Caries with Dental Fluorosis and Oral Health Behaviour Among 12-Year School Children in Moderate-Fluoride Drinking Water Community in Quetta, Pakistan. *J Coll Physicians Surg Pak.* 2016. 26:744-7	One or more exclusion criteria
L1	Eyer, F.,Zilker, T.. Caustic injuries of the eye, skin and the gastrointestinal tract. [German]. *Therapeutische Umschau.* 2009. 66:379-386	One or more exclusion criteria
L1	Olde Heuvel, J.,De Wit-Van Der Veen, L.,Stokkel, M. P. M.,Van Der Poel, H. G.,Tuch, D. S.,Grootendorst, M. R.,Vyas, K. N.,Slump, C. H.. Cerenkov luminescence imaging for intraoperative specimen analysis: A pre-clinical evaluation. *European Urology, Supplements.* 2019. 18 (1):e668-e669	One or more exclusion criteria
L1	Chen, S.,Li, B.,Lin, S.,Huang, Y.,Zhao, X.,Zhang, M.,Xia, Y.,Fang, X.,Wang, J.,Hwang, S. A.,Yu, S.. Change of urinary fluoride and bone metabolism	One or more exclusion criteria

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L1	Bennett, H. B.,Shantz, A.,Shin, G.,Sampson, M. L.,Meschke, J. S.. Characterisation of the water quality from open and rope-pump shallow wells in rural Cambodia. *Water Science & Technology.* 2010. 61:473-9	One or more exclusion criteria
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L1	Zhang, W.,Bian, J.,Yun, Z.,Cheng, P.,Sun, G.,Gao, H.,Gao, J.. Characteristics of spatial distribution of water fluoride in Heze City, Shandong Province based on inverse distance weighted. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:178-181	One or more exclusion criteria
L1	Nan, L.. Characterization and optimization of the radiochemical synthesis of [¹⁸F]AMD3465: A potential PET imaging agent for Chemokine Receptor CXCR4. *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2018. 59:#pages#	One or more exclusion criteria

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L1	Gislason, S. R.,Hassenkam, T.,Nedel, S.,Bovet, N.,Eiriksdottir, E. S.,Alfredsson, H. A.,Hem, C. P.,Balogh, Z. I.,Dideriksen, K.,Oskarsson, N.,Sigfusson, B.,Larsen, G.,Stipp, S. L. S.. Characterization of Eyjafjallajokull volcanic ash particles and a protocol for rapid risk assessment. *Proceedings of the National Academy of Sciences of the United States of America.* 2011. 108:7307-7312	One or more exclusion criteria
L1	Joseph, R.,Shelma, R.,Rajeev, A.,Muraleedharan, C. V.. Characterization of surface modified polyester fabric. *Journal of Materials Science: Materials in Medicine.* 2009. 20:S153-S159	One or more exclusion criteria
L1	Odiyo, J. O.,Makungo, R.. Chemical and Microbial Quality of Groundwater in Siloam Village, Implications to Human Health and Sources of Contamination. *Int J Environ Res Public Health.* 2018. 15:#pages#	One or more exclusion criteria
L1	Dahlin, J.,Engfeldt, M.,Svedman, C.,Mowitz, M.,Zimerson, E.,Isaksson, M.,Hindsen, M.,Bruze, M.. Chemical burns caused by trifluoroacetic acid. *Contact Dermatitis.* 2012. 2):15	One or more exclusion criteria
L1	Hsu, Y. M.,Wu, C. Y.,Lundgren, D. A.,Nall, J. W.,Birky, B. K.. Chemical characteristics of aerosol mists in phosphate fertilizer manufacturing facilities. *J Occup Environ Hyg.* 2007. 4:17-25	One or more exclusion criteria
L1	Ameer, N.,Mustafa, G.,Khan, I.,Zahid, M.,Yasinzai, M.,Shahab, S.,Asghar, N.,Ullah, I.,Ahmad, A.,Munir, I.,Khan, H.,Badshah, S.,Shahid, I.,Ahmad, M.	One or more exclusion criteria

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L1	Vilasrao, G. S.,Kamble, K. M.,Sabat, R. N.. Child fluorosis in Chhattisgarh, India: a community-based survey. *Indian Pediatr.* 2014. 51:903-5	One or more exclusion criteria
L1	Takizawa, S.,Takeda, T.,Wongrueng, A.,Wattanachira, S.. Child-education program for the reduction of health risks due to fluoride in water sources in the Chiang Mai Basin, Thailand. *Water Sci Technol.* 2010. 61:2391-7	One or more exclusion criteria
L1	Ba, Y.,Wang, G.,Yu, B.,Yang, Y. J.,Ren, L. J.,Yin, G. J.,Cheng, X. M.,Cui, L. X.,Zhang, Y. W.. Children's dental fluorosis and estrogen receptor alpha gene Xba I polymorphism. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:278-281	One or more exclusion criteria
L1	Cherry, D. C.,Huggins, B.,Gilmore, K.. Children's Health in the Rural Environment. *Pediatric Clinics of North America.* 2007. 54:121-133	One or more exclusion criteria
L1	Kanagaraj, G.,Elango, L.. Chromium and fluoride contamination in groundwater around leather tanning industries in southern India: Implications from stable	One or more exclusion criteria

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L1	Rao, T. K.,Kasiviswanath, I. V.,Murthy, Y. L. N.. Defluoridation of water by nanotechnology. *Water Science and Technology: Water Supply.* 2009. 9:485-492	One or more exclusion criteria

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L1	Rah, J. E.,Oh, D. H.,Shin, D.,Kim, D. H.,Ji, Y. H.,Kim, J. W.,Park, S. Y.. Dosimetric evaluation of a glass dosimeter for proton beam measurements. *Appl Radiat Isot.* 2012. 70:1616-23	One or more exclusion criteria
L1	Sweileh, W. M.,Zyoud, S. H.,Al-Jabi, S. W.,Sawalha, A. F.,Shraim, N. Y.. Drinking and recreational water-related diseases: a bibliometric analysis (1980-2015). *Ann Occup Environ Med.* 2016. 28:40	One or more exclusion criteria
L1	Mastrantonio, M.,Bai, E.,Uccelli, R.,Cordiano, V.,Screpanti, A.,Crosignani, P.. Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. *Eur J Public Health.* 2018. 28:180-185	One or more exclusion criteria
L1	Comber, H.,Deady, S.,Montgomery, E.,Gavin, A.. Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. *Cancer Causes Control.* 2011. 22:919-24	One or more exclusion criteria
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L1	Narsimha, A.,Sudarshan, V.. Drinking water pollution with respective of fluoride in the semi-arid region of Basara, Nirmal district, Telangana State, India. *Data Brief.* 2018. 16:752-757	One or more exclusion criteria
L1	Wasana, H. M.,Aluthpatabendi, D.,Kularatne, W. M.,Wijekoon, P.,Weerasooriya, R.,Bandara, J.. Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. *Environ Geochem Health.* 2016. 38:157-68	One or more exclusion criteria
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L1	Beaudeau, P.,Schwartz, J.,Levin, R.. Drinking water quality and hospital admissions of elderly people for gastrointestinal illness in Eastern Massachusetts, 1998-2008. *Water Research.* 2014. 52:188-198	One or more exclusion criteria
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L1	Xia, Y. T.,Wang, Y.,Wang, P. H.,Wang, C. S.,Shu, C. L.,Wu, J.. Drinking-water type endemic fluorosis in Northern Jiangsu Province in 2008: An analysis of survey results. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:434-436	One or more exclusion criteria
L1	Fan, Z. X.,Li, Y.,Li, X. Q.,Bai, G. L.,Liu, X. L.,Bai, A. M.,Li, P. A.,Yang, X. D.. Drinking-water type of fluorosis in Shaanxi province in 2009: An analysis of surveillance results. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:294-297	One or more exclusion criteria
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L1	Zurita, J. L.,Jos, A.,Cameán, A. M.,Salguero, M.,López-Artíguez, M.,Repetto, G.. Ecotoxicological evaluation of sodium fluoroacetate on aquatic organisms and investigation of the effects on two fish cell lines. *Chemosphere.* 2007. 67:1-12	One or more exclusion criteria
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L1	Hammouda, I. M.,Al-Wakeel, E. E.. Effect of water storage on fluoride release and mechanical properties of a polyacid-modified composite resin (compomer). *Journal of Biomedical Research.* 2011. 25:254-258	One or more exclusion criteria
L1	Antoniazzi, R. P.,Machado, M. E.,Grellmann, A. P.,Santos, R. C.,Zanatta, F. B.. Effectiveness of a desensitizing agent for topical and home use for dentin hypersensitivity: a randomized clinical trial. *Am J Dent.* 2014. 27:251-7	One or more exclusion criteria
L1	Anthoney, D.,Zahid, S.,Khalid, H.,Khurshid, Z.,Shah, A. T.,Chaudhry, A. A.,Khan, A. S.. Effectiveness of Thymoquinone and Fluoridated Bioactive Glass/Nano-Oxide Contained Dentifrices on Abrasion and Dentine Tubules Occlusion: An Ex Vivo Study. *Eur J Dent.* 2020. 14:45-54	One or more exclusion criteria
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L1	Sushma Susik, M. S.,Ajay Prakash, P.,Madhusudhan Rao, T.. Effects of different concentrations of fluoride in oral mucosal cells in albino rats. *J Clin Diagn Res.* 2015. 9:ZF01-ZF04	One or more exclusion criteria
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L1	Shaffer, J. R.,Carlson, J. C.,Stanley, B. O. C.,Feingold, E.,Cooper, M.,Vanyukov, M. M.,Maher, B. S.,Slayton, R. L.,Willing, M. C.,Reis, S.	One or more exclusion criteria

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L1	Goyal, N.,Dulawat, M. S.,Dulawat, S. S.. Effects of fluoride on human health in Rajasthan. *Advanced Science, Engineering and Medicine.* 2019. 11:21-23	One or more exclusion criteria
L1	Zhang, Y.,Xie, L.,Li, X.,Chai, L.,Chen, M.,Kong, X.,Wang, Q.,Liu, J.,Zhi, L.,Yang, C.,Wang, H.. Effects of fluoride on morphology, growth, development, and thyroid hormone of Chinese toad (Bufo gargarizans) embryos. *Environ Mol Mutagen.* 2018. 59:123-133	One or more exclusion criteria

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L1	Park, E. Y.,Hwang, S. S.,Kim, J. Y.,Cho, S. H.. Effects of long-term fluoride in drinking water on risks of hip fracture of the elderly: an ecologic study based on database of hospitalization episodes. [Korean]. *Journal of preventive medicine and public health = Yebang Uihakhoe chi.* 2008. 41:147-152	One or more exclusion criteria
L1	Cai, J.,Burrow, M. F.,Manton, D. J.,Tsuda, Y.,Sobh, E. G.,Palamara, J. E. A.. Effects of silver diamine fluoride/potassium iodide on artificial root caries lesions with adjunctive application of proanthocyanidin. *Acta Biomaterialia.* 2019. 88:491-502	One or more exclusion criteria
L1	Khandare, A.,Rasaputra, K.,Meshram, I.,Rao, S.. Effects of smoking, use of aluminium utensils, and tamarind consumption on fluorosis in a fluorotic village of Andhra Pradesh, India. *Fluoride.* 2010. 43:128-133	One or more exclusion criteria
L1	Andrade-Vieira, L. F.,de Campos, J. M. S.,Davide, L. C.. Effects of Spent Pot Liner on mitotic activity and nuclear DNA content in meristematic cells of Allium cepa. *Journal of Environmental Management.* 2012. 107:140-146	One or more exclusion criteria
L1	Zhang, X. J.,Sun, T. C.,Liu, Z. W.,Wang, F. J.,Wang, Y. D.,Liu, J.. Effects of Tianmagouteng particles on brain cognitive function in spontaneously	One or more exclusion criteria

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L1	Daumar, P.,Wanger-Baumann, C. A.,Pillarsetty, N.,Fabrizio, L.,Carlin, S. D.,Andreev, O. A.,Reshetnyak, Y. K.,Lewis, J. S.. Efficient (18)F-labeling of large 37-amino-acid pHLIP peptide analogues and their biological evaluation. *Bioconjug Chem.* 2012. 23:1557-66	One or more exclusion criteria
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L1	Brandt Jr, E. N.. Endemic fluorosis and its relation to dental caries (1938): Commentary. *Public Health Reports.* 2006. 121:212-219	One or more exclusion criteria
L1	Srikanth, R.,Chandra, T. R.,Kumar, B. R.. Endemic fluorosis in five villages of the Palamau District, Jharkhand, India. *Fluoride.* 2008. 41:206-211	One or more exclusion criteria

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L1	Zheng, Z. X.,Liu, W.,Zhao, W. G.,Lin, S. G.,Wang, H.. Endemic flurosis: Current status of prevention and control in Liaoning. [Chinese]. *Chinese Journal of Endemiology.* 2006. 25:328-329	One or more exclusion criteria
L1	Petrone, P.,Giordano, M.,Giustino, S.,Guarino, F. M.. Enduring fluoride health hazard for the Vesuvius area population: the case of AD 79 Herculaneum. *PLoS One.* 2011. 6:e21085	One or more exclusion criteria
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L1	Cardenas-Gonzalez, M.,Osorio-Yanez, C.,Gaspar-Ramirez, O.,Pavkovic, M.,Ochoa, Martinez,Lopez-Ventura, D.,Medeiros, M.,Barbier, O.,Perez-	One or more exclusion criteria

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L1	Etzel, R. A.. Environmental hazards that matter for children's health. *Hong Kong Journal of Paediatrics.* 2015. 20:86-94	One or more exclusion criteria
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L1	Buchhamer, E. E.,Blanes, P. S.,Osicka, R. M.,Giménez, M. C.. Environmental risk assessment of arsenic and fluoride in the Chaco Province, Argentina: research advances. *J Toxicol Environ Health A.* 2012. 75:1437-50	One or more exclusion criteria

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L1	Lowe, P. T.,Dall'Angelo, S.,Fleming, I. N.,Piras, M.,Zanda, M.,O'Hagan, D.. Enzymatic radiosynthesis of a (18)F-Glu-Ureido-Lys ligand for the prostate-specific membrane antigen (PSMA). *Org Biomol Chem.* 2019. 17:1480-1486	One or more exclusion criteria
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L1	Wei, S.,Lu, Q.,Yang, P.,Li, S.,Jiang, H.,Chen, P.,La, C.,He, D.,Wu, H.. Epidemic status of drinking-tea-borne fluorosis in different occupational groups in Qinghai Province. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:164-166	One or more exclusion criteria
L1	Chen, P. Z.,Yun, Z. J.,Gao, H. X.,Ma, A. H.,Wang, Y. T.,Li, H. X.,Zhao, L. J.. Epidemiologic studies of endemic fluorosis in Jiaxiang. A county in Shandong province. [Chinese]. *Chinese Journal of Endemiology.* 2006. 25:537-540	One or more exclusion criteria
L1	Chen, P. Z.,Yun, Z. J.,Gao, H. X.,Li, H. X.,Wang, Y. T.,Gao, J.,Yin, Y. Y.. Epidemiological investigation and analysis of water-related endemic fluorosis in the south area of Shandong province in 2009. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:566-570	One or more exclusion criteria

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L1	Yun, Z. J.,Chen, P. Z.,Bian, J. C.,Wang, Y. T.,Gao, J.,Yin, Y. Y.,Li, H. X.,Liu, Y.. Epidemiological investigation of endemic fluorosis of Shandong province in 2010. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:571-575	One or more exclusion criteria
L1	Yun, Z. J.,Bian, J. C.,Chen, P. Z.,Pang, X. G.,Wang, Y. T.,Li, H. X.,Zhao, L. J.,Gao, Y. M.,Zhang, S. X.,Zhou, C. K.. Epidemiological investigation on endemic fluorosis in Boxing County of Shandong Province in 2007. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:75-77	One or more exclusion criteria
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L1	McLaku, Z.,Assefa, G.,Enqusilassie, F.,Bjorvatn, K.,Tekle-Haimanot, R.. Epidemiology of skeletal fluorosis in wonji shoa sugar estate, wonji, ethiopia: A community based survey. *Ethiopian Medical Journal.* 2012. 50:307-313	One or more exclusion criteria

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L1	Wimalawansa, S. J.. Escalating chronic kidney diseases of multi-factorial origin (CKD-mfo) in Sri Lanka: causes, solutions, and recommendations-update and responses. *Environmental Health and Preventive Medicine.* 2015. 20:152-157	One or more exclusion criteria
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L1	Awofeso, N.. Ethics of artificial water fluoridation in Australia. *Public Health Ethics.* 2012. 5:161-172	One or more exclusion criteria

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L1	Jiménez-Córdova, M. I.,Cárdenas-González, M.,Aguilar-Madrid, G.,Sanchez-Peña, L. C.,Barrera-Hernández, Á,Domínguez-Guerrero, I. A.,González-Horta, C.,Barbier, O. C.,Del Razo, L. M.. Evaluation of kidney injury biomarkers in an adult Mexican population environmentally exposed to fluoride and low arsenic levels. *Toxicol Appl Pharmacol.* 2018. 352:97-106	One or more exclusion criteria
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L1	Willekens, I.,Buls, N.,Lahoutte, T.,Baeyens, L.,Vanhove, C.,Caveliers, V.,Deklerck, R.,Bossuyt, A.,de Mey, J.. Evaluation of the radiation dose in	One or more exclusion criteria

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L1	Nelson, E. A.,Halling, C. L.. Evidence for skeletal fluorosis in Illinois: A pathological analysis of individuals from the ray site and discussion of environmental factors affecting community health. *American Journal of Physical Anthropology.* 2014. 58):193	One or more exclusion criteria
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L1	Huber, A. C.,Tobias, R.,Mosler, H. J.. Evidence-based tailoring of behavior-change campaigns: increasing fluoride-free water consumption in rural Ethiopia with persuasion. *Applied Psychology. Health and Well-being.* 2014. 6:96-118	One or more exclusion criteria
L1	Chakraborti, D.,Das, B.,Murrill, M. T.. Examining India's groundwater quality management. *Environmental Science and Technology.* 2011. 45:27-33	One or more exclusion criteria

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L1	Al-Raddadi, R. M.,Bahijri, S. M.,Al-Khateeb, T.. Excessive fluoride intake is associated with hyperparathyroidism and hypothyroidism in children and adolescent, Jeddah-Saudi Arabia. *Archives of Disease in Childhood.* 2012. 2):A294	One or more exclusion criteria
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L1	Susheela, A. K.,Mondal, N. K.,Singh, A.. Exposure to fluoride in smelter workers in a primary aluminum industry in India. *Int J Occup Environ Med.* 2013. 4:61-72	One or more exclusion criteria
L1	Zhang, Y. L.,Zhao, Y.,Tang, L.,Wu, Q. Q.,Bai, S. B.,Zhong, J. J.. Expression of minichromosome maintenance 3 from the peripheral blood of fluorosis patients and the liver and renal function. [Chinese]. *Chinese Journal of Tissue Engineering Research.* 2013. 17:6682-6688	One or more exclusion criteria
L1	Claassen, H.,Cellarius, C.,Scholz-Ahrens, K. E.,Schrezenmeir, J.,Gluer, C. C.,Schunke, M.,Kurz, B.. Extracellular matrix changes in knee joint cartilage following bone-active drug treatment. *Cell and Tissue Research.* 2006. 324:279-289	One or more exclusion criteria

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L1	Rocha, R. A.,de la Fuente, B.,Clemente, M. J.,Ruiz, A.,Vélez, D.,Devesa, V.. Factors affecting the bioaccessibility of fluoride from seafood products. *Food Chem Toxicol.* 2013. 59:104-10	One or more exclusion criteria
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L1	Ozsoy, G.,Kendirli, T.,Ates, U.,Perk, O.,Azapagasi, E.,Ozcan, S.,Baran, C.,Goktug, A.,Dindar, H.. Fatal Refractory Ventricular Fibrillation Due to Ingestion of Hydrofluoric Acid. *Pediatric Emergency Care.* 2019. 35:E201-E202	One or more exclusion criteria
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L1	Dias, I. N.,Bassin, J. P.,Dezotti, M.,Vilar, V. J. P.. Fluorene oxidation by solar-driven photo-Fenton process: toward mild pH conditions. *Environ Sci Pollut Res Int.* 2018. 25:27808-27818	One or more exclusion criteria

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L1	Foley, M.. Fluoridation and hypothyroidism--a commentary on Peckham et al. *Br Dent J.* 2015. 219:429-31	One or more exclusion criteria
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L1	Borman, B.,Fyfe, C.. Fluoride and children's IQ. *N Z Med J.* 2013. 126:111-2	One or more exclusion criteria
L1	Lewis, C. W.. Fluoride and dental caries prevention in children. *Pediatrics in Review.* 2014. 35:3-15	One or more exclusion criteria

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L1	Hussain, J.,Hussain, I.,Sharma, K. C.. Fluoride and health hazards: community perception in a fluorotic area of central Rajasthan (India): an arid environment. *Environ Monit Assess.* 2010. 162:1-14	One or more exclusion criteria
L1	Chachra, D.,Vieira, A. P.,Grynpas, M. D.. Fluoride and mineralized tissues. *Crit Rev Biomed Eng.* 2008. 36:183-223	One or more exclusion criteria
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L1	Vitoria Minana, I.. Fluoride and the prevention of dental caries in childhood. Update (I). [Spanish]. *Acta Pediatrica Espanola.* 2010. 68:129-134	One or more exclusion criteria
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L1	Palczewska-Komsa, M.,Kalisinska, E.,Kosik-Bogacka, D.,Lanocha-Arendarczyk, N.,Budis, H.,Sokolowski, S.,Baranowska-Bosiacka, I.,Gutowska, I.,Chlubek, D.. Fluoride in the compact bone after femoral head arthroplasty in patients from North-Western Poland. *Fluoride.* 2015. 48:93-104	One or more exclusion criteria

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L1	Peckham, S.,Lowery, D.,Spencer, S.. Fluoride levels in drinking water and hypothyroidism: Response to Grimes and Newton et al. *J Epidemiol Community Health.* 2017. 71:313-314	One or more exclusion criteria
L1	Ravichandran, B.,Bhattacharya, S. K.,Mukherjee, A. K.,Gangopadhyay, P. K.,Roychowdhury, A.,Saiyed, H. N.. Fluoride levels in drinking water and other surface water of an industrial area belt of Orissa State in India. *International Journal of Environment and Pollution.* 2012. 49:55-61	One or more exclusion criteria
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L1	Lacson, C. F. Z.,Lu, M. C.,Huang, Y. H.. Fluoride network and circular economy as potential model for sustainable development-A review. *Chemosphere.* 2020. 239 (no pagination):#pages#	One or more exclusion criteria

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L1	Rashid, A.,Guan, D. X.,Farooqi, A.,Khan, S.,Zahir, S.,Jehan, S.,Khattak, S. A.,Khan, M. S.,Khan, R.. Fluoride prevalence in groundwater around a fluorite mining area in the flood plain of the River Swat, Pakistan. *Sci Total Environ.* 2018. 635:203-215	One or more exclusion criteria
L1	De Oliveira, F. A.,Pereira, A. A.,Da Silva Ventura, T.,Buzalaf, M.,De Oliveira, R. C.,Peres-Buzalaf, C.. Fluoride regulates osteoclastogenesis in a strain-specific manner. *Journal of Bone and Mineral Research. Conference.* 2016. 31:#pages#	One or more exclusion criteria
L1	Seraoui, H.. Fluoride remedy or poison?. *Fundamental and Clinical Pharmacology.* 2014. 1):112	One or more exclusion criteria
L1	Bazrafshan, E.,Mahvi, A. H.. Fluoride removal by an electro-coagulation using iron and aluminum electrodes. *Fluoride.* 2012. 45 (3 PART 1):154-155	One or more exclusion criteria
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L1	Mena, V. F.,Betancor-Abreu, A.,Gonzalez, S.,Delgado, S.,Souto, R. M.,Santana, J. J.. Fluoride removal from natural volcanic underground water by an electrocoagulation process: Parametric and cost evaluations. *Journal of Environmental Management.* 2019. 246:472-483	One or more exclusion criteria
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L1	Garg, V. K.,Singh, B.. Fluoride signatures in groundwater and dental fluorosis in permanent teeth of school children in rural areas of Haryana state, india. *International Journal of Occupational and Environmental Medicine.* 2013. 4:107-108	One or more exclusion criteria
L1	Abell, S.. Fluoride supplementation. *Clinical Pediatrics.* 2008. 47:91-92	One or more exclusion criteria
L1	Takahashi, R.,Ota, E.,Hoshi, K.,Naito, T.,Toyoshima, Y.,Yuasa, H.,Mori, R.,Nango, E.. Fluoride supplementation (with tablets, drops, lozenges or	One or more exclusion criteria

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L1	Clark, M. B.,Slayton, R. L.. Fluoride use in caries prevention in the primary care setting. *Pediatrics.* 2014. 134:626-633	One or more exclusion criteria
L1	Dutta, J.. Fluoride, arsenic and other heavy metals contamination of drinking water in the tea garden belt of sonitpur district, Assam, India. *International Journal of ChemTech Research.* 2013. 5:2614-2622	One or more exclusion criteria
L1	Spittle, B.. Fluoride, IQ, emotion, and children's school performance. *Fluoride.* 2018. 51:98-101	One or more exclusion criteria
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L1	Spittle, B.. Fluoride-induced developmental disorders and iodine deficiency disorders as examples developmental disorders due to disturbed thyroid hormone metabolism. *Fluoride.* 2018. 51:307-318	One or more exclusion criteria
L1	Ramirez, D. I.,Vargas-Sierra, O.,Flores-Mendez, M. A.,Hernandez-Kelly, L. C.,Del Razo, L. M.,Ortega, A.. Fluoride-triggered protein synthesis decrease in cerebellar Bergmann glia cells. *Journal of Neurochemistry.* 2013. 1):117	One or more exclusion criteria
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L1	Whittier, K.,Martin, M.,O'Dorisio, M. S.,Tewson, T.. Fluorination of GDC-0449 as a PET tracer in medulloblastoma. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2013. 1):S149	One or more exclusion criteria

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L1	Hong, M.,Zhang, B.,Zhang, X. I.,Zhao, Y. S.. Fluorine distribution in aquatic environment and its health effect in the Western Region of the Songnen Plain, Northeast China. *Environmental Monitoring and Assessment.* 2007. 133:379-386	One or more exclusion criteria
L1	Zhang, B.,Hong, M.,Zhang, B.,Zhang, X. L.,Zhao, Y. S.. Fluorine distribution in aquatic environment and its health effect in the Western Region of the Songnen Plain, Northeast China. *Environmental Monitoring & Assessment.* 2007. 133:379-86	One or more exclusion criteria
L1	Chae, G. T.,Yun, S. T.,Mayer, B.,Kim, K. H.,Kim, S. Y.,Kwon, J. S.,Kim, K.,Koh, Y. K.. Fluorine geochemistry in bedrock groundwater of South Korea. *Science of the Total Environment.* 2007. 385:272-283	One or more exclusion criteria
L1	De Rita, D.,Cremisini, C.,Cinnirella, A.,Spaziani, F.. Fluorine in the rocks and sediments of volcanic areas in central Italy: Total content, enrichment and leaching processes and a hypothesis on the vulnerability of the related aquifers. *Environmental Monitoring and Assessment.* 2012. 184:5781-5796	One or more exclusion criteria

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L1	Kuhnast, B.,Maisonial, A.,Hinnen, F.,Boisgard, R.,Chezal, J.,Moins, N.,Madelmont, J.,Tavitian, B.,Dolle, F.. Fluorine-18 labeling of a new melanin-targeting tracer for melanoma imaging with PET. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2009. 1):S131	One or more exclusion criteria
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L1	Dey, R. K.,Swain, S. K.,Mishra, S.,Sharma, P.,Patnaik, T.,Singh, V. K.,Dehury, B. N.,Jha, U.,Patel, R. K.. Hydrogeochemical processes controlling the high fluoride concentration in groundwater: A case study at the Boden block area, Orissa, India. *Environmental Monitoring and Assessment.* 2012. 184:3279-3291	One or more exclusion criteria
L1	Mitchell, S. M.,Ullman, J. L.,Teel, A. L.,Watts, R. J.. Hydrolysis of amphenicol and macrolide antibiotics: Chloramphenicol, florfenicol, spiramycin, and tylosin. *Chemosphere.* 2015. 134:504-11	One or more exclusion criteria
L1	Lepoittevin, B.,Elzein, T.,Dragoe, D.,Bejjani, A.,Lemee, F.,Levillain, J.,Bazin, P.,Roger, P.,Dez, I.. Hydrophobization of chitosan films by surface grafting with fluorinated polymer brushes. *Carbohydrate polymers.* 2019. 205:437-446	One or more exclusion criteria
L1	Tredwin, C. J.,Young, A. M.,Abou Neel, E. A.,Georgiou, G.,Knowles, J. C.. Hydroxyapatite, fluor-hydroxyapatite and fluorapatite produced via the sol-gel method: dissolution behaviour and biological properties after crystallisation. *J Mater Sci Mater Med.* 2014. 25:47-53	One or more exclusion criteria
L1	Ramamoorthy, N.,Pillai, M. R. A.,Jin, J. H.,Haji-Saeid, S. M.. IAEA activities in support of production and utilization of radioisotope labelled compounds. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2007. 50:312-317	One or more exclusion criteria
L1	Iarc Working Group on the Evaluation of Carcinogenic Risk to Humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *Some*	One or more exclusion criteria

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L1	Tang, Y. S. C.,Davis, R. A.,Ganguly, T.,Sutcliffe, J. L.. Identification, Characterization, and Optimization of Integrin α(v)β_6-Targeting Peptides from a One-Bead One-Compound (OBOC) Library: Towards the Development of Positron Emission Tomography (PET) Imaging Agents. *Molecules.* 2019. 24:#pages#	One or more exclusion criteria
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L1	Gai, Y.,Yuan, L.,Li, H.,Zeng, D.,Lan, X.. Imaging of melanoma Using Al¹⁸F labeled peptidomemitic ligand LLP2A. *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2018. 59:#pages#	One or more exclusion criteria

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L1	Frawley, R. P.,Smith, M.,Cesta, M. F.,Hayes-Bouknight, S.,Blystone, C.,Kissling, G. E.,Harris, S.,Germolec, D.. Immunotoxic and hepatotoxic effects of perfluoro-n-decanoic acid (PFDA) on female Harlan Sprague-Dawley rats and B₆C₃F₁/N mice when administered by oral gavage for 28 days. *Journal of Immunotoxicology.* 2018. 15:41-52	One or more exclusion criteria
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L1	Shankar, B. S.,Balasubramanya, N.,Maruthesha Reddy, M. T.. Impact of industrialization on groundwater quality--a case study of Peenya industrial area, Bangalore, India. *Environ Monit Assess.* 2008. 142:263-8	One or more exclusion criteria
L1	Grover, P. K.,Kaur, K.,Gautam, C. S.. Impact of milk intake on dental fluorosis in the North Indian population: An observational study. *Biomedicine (India).* 2018. 38:190-194	One or more exclusion criteria
L1	Bhagat, S. K.,Tiyasha,. Impact of millions of tones of effluent of textile industries: Analysis of textile industries effluents in Bhilwara and an approach	One or more exclusion criteria

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L1	Ahmad, F.. Impact of urbanization on groundwater quality of Bhagalpur city: Deterioration of water quality and its sustainable management. *Journal of Chemical and Pharmaceutical Research.* 2015. 7:1303-1307	One or more exclusion criteria
L1	Ahoyo, T. A.,Fatombi, K. J.,Boco, M.,Aminou, T.,Bramane, K. L.. Impact of water quality and environmental sanitation on the health of schoolchildren in a suburban area of Benin: Findings in the Savalou-Bante and Dassa-Glazoue sanitary districts. [French]. *Medecine Tropicale.* 2011. 71:281-285	One or more exclusion criteria
L1	Mula, A.,Skrobanska, A.,Nowis, D.. Impairment of glucose uptake in cancer cells by statins. *European Journal of Medical Research.* 2011. 1):40-41	One or more exclusion criteria
L1	Berroteran-Infante, N.,Hacker, M.,Mitterhauser, M.,Wadsak, W.. Improved automated radiosynthesis of [¹⁸F]FEPPA. *EJNMMI Radiopharmacy and Chemistry. Conference: 18th European Symposium on Radiopharmacy and Radiopharmaceuticals. Austria..* 2016. 1:#pages#	One or more exclusion criteria
L1	Vavere, A. L.,Hu, B.,Neumann, K. D.,DiMagno, S. G.,Snyder, S. E.. Improved synthesis and purification of meta-[¹⁸F]fluorobenzylguanidine (mFBG) for clinical use. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2015. 1):S216	One or more exclusion criteria

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L1	Qu, W.,Kelly, J.,Amor-Coarasa, A.,Waterhouse, N.,Dooley, M.,Babich, J.. Improved two-step click synthesis of [¹⁸F]RPS-040: A prostate specific membrane antigen (PSMA)-targeted tracer for Imaging prostate cancer (PCa) using positron emission tomography (PET). *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2018. 59:#pages#	One or more exclusion criteria
L1	Fitz, N. F.,Castranio, E. L.,Carter, A. Y.,Kodali, R.,Lefterov, I.,Koldamova, R.. Improvement of memory deficits and amyloid-β clearance in aged APP23 mice treated with a combination of anti-amyloid-β antibody and LXR agonist. *J Alzheimers Dis.* 2014. 41:535-49	One or more exclusion criteria
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L1	Seong, J.,Macdonald, E.,Newcombe, R. G.,Davies, M.,Jones, S. B.,Johnson, S.,West, N. X.. In situ randomised trial to investigate the occluding properties of two desensitising toothpastes on dentine after subsequent acid challenge. *Clin Oral Investig.* 2013. 17:195-203	One or more exclusion criteria
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L1	Lütje, S.,Franssen, G. M.,Herrmann, K.,Boerman, O. C.,Rijpkema, M.,Gotthardt, M.,Heskamp, S.. In Vitro and In Vivo Characterization of an (18)F-AlF-Labeled PSMA Ligand for Imaging of PSMA-Expressing Xenografts. *J Nucl Med.* 2019. 60:1017-1022	One or more exclusion criteria
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L1	Huang, Y.,Tsai, C.,Ho, B.,Ho, H.,Chang, Y.,Wu, C.,Yen, R.,Shiue, C.. In vitro evaluation of [¹⁸F]FPA as a fatty acid synthasetargeting imaging agent for breast cancer and its in vivo whole-body biodistribution in normal mice. *European Journal of Nuclear Medicine and Molecular Imaging.* 2019. 46 (1 Supplement 1):S709-S710	One or more exclusion criteria
L1	Krisanapun, C.,Wongkrajang, Y.,Temsiririrkkul, R.,Phornchirasilp, S.,Peungvicha, P.. In vitro evaluation of anti-diabetic potential of piper sarmentosum Roxb. extract. *FASEB Journal. Conference: Experimental Biology.* 2012. 26:#pages#	One or more exclusion criteria
L1	Mehta, D.,Mondal, P.,Saharan, V. K.,George, S.. In-vitro synthesis of marble apatite as a novel adsorbent for removal of fluoride ions from ground water: An ultrasonic approach. *Ultrasonics Sonochemistry.* 2018. Part A. 40:664-674	One or more exclusion criteria
L1	A, S.,M, K.,M, B.. Incidence of skeletal deformities in endemic fluorosis. *Trop Doct.* 2008. 38:231-3	One or more exclusion criteria
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L1	Lepri, C. P.,Geraldo-Martins, V. R.,Faraoni-Romano, J. J.,Palma-Dibb, R. G.. Influence of different lasers irradiation, associated or not to fluoride, on root caries prevention. *Medicina Oral, Patologia Oral y Cirugia Bucal.* 2012. 17 (SUPPL.1):S181	One or more exclusion criteria
L1	Resende, R. F.,Arantes, B. F.,Palma-Dibb, R. G.,Faraoni, J. J.,de Castro, D. T.,de Menezes Oliveira, M. A. H.,Soares, C. J.,Geraldo-Martins, V. R.,Lepri, C.	One or more exclusion criteria

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L1	Povoroznyuk, V. V.,Grygoreva, N. V.,Vilensky, A. V.,Dmitrenco, O. P.. Influence of raised fluorine concentrations in water on structurally-functional state of bone mass, teeth, anthropometric parameters and physical development of teenagers. *Bone.* 2009. 2):S76-S77	One or more exclusion criteria
L1	Alehosseini, M.,Edris, H.,Fathi, M.. Influence of strontium on the structure and biological properties of mechanical activation sr-doped flourapatite nanopowder for bone replacement. *Iranian Journal of Biotechnology.* 2017. ISSUE):115	One or more exclusion criteria
L1	Iglesias-Jerez, R.,Cayero-Otero, M. D.,Martin-Banderas, L.,Borrego-Dorado, I.. Influence of the use of cryoprotectant on the ladiolabelling of poly(lactic-co-glycolic acid) (PLGA) nanoparticles with 99m Tc. *European Journal of Nuclear Medicine and Molecular Imaging.* 2017. 44 (2 Supplement 1):S564	One or more exclusion criteria
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L1	Dimachkie, P.,Peicher, K.,Maalouf, N. M.. Inhalation of air dust cleaner causing skeletal fluorosis. *Endocrine Reviews. Conference: 99th Annual Meeting of the Endocrine Society, ENDO.* 2017. 38:#pages#	One or more exclusion criteria
L1	A, S.,G, M.. Inhibitory Effect of Fluoride on Na+,K+ ATPase Activity in Human Erythrocyte Membrane. *Biological Trace Element Research.* 2015. 168:340-8	One or more exclusion criteria
L1	Zhang, Y.,Zhang, L.,Yang, J.,Wu, Z.,Ploessl, K.,Zha, Z.,Liu, F.,Xu, X.,Zhu, H.,Yang, Z.,Zhu, L.,Kung, H. F.. Initial experience in synthesis of (2S,4R)-4-[(18) F]fluoroglutamine for clinical application. *J Labelled Comp Radiopharm.* 2019. 62:209-214	One or more exclusion criteria
L1	Russo, F.,Ursino, C.,Avruscio, E.,Desiderio, G.,Perrone, A.,Santoro, S.,Galiano, F.,Figoli, A.. Innovative Poly (Vinylidene Fluoride) (PVDF) Electrospun Nanofiber Membrane Preparation Using DMSO as a Low Toxicity Solvent. *Membranes (Basel).* 2020. 10:#pages#	One or more exclusion criteria
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L1	Podder, S.,Ghoshal, N.,Banerjee, A.,Ganguly, B.,Upadhyay, R.,Chatterjee, A.. Interaction of DNA-lesions induced by sodium fluoride and radiation and its influence in apoptotic induction in cancer cell lines. *Toxicol Rep.* 2015. 2:461-471	One or more exclusion criteria
L1	Spittle, B.. International differences in the recognition of non-skeletal Fluorosis: A comparison of India and New Zealand. *Fluoride.* 2018. 51:199-205	One or more exclusion criteria
L1	Bai, S. Y.,Xu, J. M.,Dao, L. T.,Jia, J. X.,Liu, M. L.,Wang, W. H.. Intervened observation of low-fluoride brick-tea on the population in drinking-tea type fluorosis areas in Akesai County of Gansu Province. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:429-432	One or more exclusion criteria
L1	Rehman, A. U.,Rafique, W.,Mehmood, M.,Bashir, M.,Ali, B.,Nawaz, M. K.,Faruqui, Z. S.,Gilani, S. A. N.. Introduction of Pakistan 1st Cyclotron & PET/CT Centre. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2011. 1):S132	One or more exclusion criteria

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L1	Li, J.,Liang, P.,Zheng, L.. Investigation and analysis on the fluorine source and fluorotic teeth epidemic factors in wumeng mountain coal-burning contaminated area. *Biomedical Research (India).* 2017. 2017:S187-S192	One or more exclusion criteria
L1	Ge, P. F.,Yu, S. Q.,Shao, J. Y.,Liao, Y. J.,Wang, W. L.,Bai, S. Y.,Ren, Y. G.,Jia, J. X.. Investigation and distribution of higher fluorides water in different ecotypic areas in Gansu Province from 2006 to 2008. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:633-636	One or more exclusion criteria
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L1	Yang, Z. M.,Zhang, L.,Yang, D. Q.,Wu, Z. J.,Yu, L.. Investigation on coal-burning fluorosis in mineral factory areas of Hongya Cunty, Sichuan Province. [Chinese]. *Chinese Journal of Endemiology.* 2007. 26:557-559	One or more exclusion criteria
L1	Wang, L. H.,Liu, L. Z.,Shi, Y. X.,Gao, Y. H.,Liu, Y. Q.,Sun, D. J.. Investigation on histopathological damages of articular growth plate cartilage, liver and kidney of rats with fluorosis induced by drinking brick-tea in the high altitude areas. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:25-29	One or more exclusion criteria
L1	Chen, J. A.,Lan, T. S.,Chen, Z. H.,Lan, Y. G.,Zhang, Z. C.,Chen, H. Q.,Qiu, Q. R.,Chen, J. X.. Investigation on prevailing factors synthesized control measures of endemic fluorosis in Longyan City. [Chinese]. *Chinese Journal of Endemiology.* 2007. 26:699-701	One or more exclusion criteria

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L1	Chen, P. Z.,Yun, Z. J.,Bian, J. C.,Li, H. X.,Gao, H. X.,Ma, A. H.,Wang, Y. T.,Zhao, L. J.,Song, S. L.. Investigation on the prevention and control of endemic fluorosis in the southwestern area of Shandong province in 2007. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:186-189	One or more exclusion criteria
L1	Gao, H. X.,Wang, Y. T.,Wang, Z. Z.,Lu, X. D.,Li, T.,Zhao, L. J.. Investigation on water fluoride content and water-improving defluoridation projects in endemic fluorosis areas in Jining City, Shandong Province in 2005. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:526-528	One or more exclusion criteria
L1	Hoscan, M. B.,Dilmen, C.,Ekinci, M.,Oksay, T.,Orak, S.,Bedir, S.,Serel, T. A.. Invitro effects of our spring water on the solubility of uric acid stones: A pilot study. [Turkish]. *Journal of Clinical and Analytical Medicine.* 2010. 1:15-17	One or more exclusion criteria
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L1	Cox, C. D.,Breslin, M. J.,Whitman, D. B.,Coleman, P. J.,Garbaccio, R. M.,Fraley, M. E.,Zrada, M. M.,Buser, C. A.,Walsh, E. S.,Hamilton, K.,Lobell, R. B.,Tao, W.,Abrams, M. T.,South, V. J.,Huber, H. E.,Kohl, N. E.,Hartman, G. D.. Kinesin spindle protein (KSP) inhibitors. Part V: discovery of 2-propylamino-2,4-diaryl-2,5-dihydropyrroles as potent, water-soluble KSP inhibitors, and modulation of their basicity by beta-fluorination to overcome cellular efflux by P-glycoprotein. *Bioorg Med Chem Lett.* 2007. 17:2697-702	One or more exclusion criteria
L1	Qiu, L.,Xie, M.,Lin, J.. Kit-like 18F radiolabeling of caspase activatable molecular probe for in situ noninvasive imaging of drug-induced apoptosis. *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2018. 59:#pages#	One or more exclusion criteria
L1	Ly, P.,Hayes, D. K.,Yamashiroya, V.,Turnure, M. M.,Iwaishi, L. K.. Knowledge and Attitudes Towards Fluoride Supplementation: A Survey of Pediatric	One or more exclusion criteria

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L1	Bottenberg, P.,Melckebeke, L. V.,Louckx, F.,Vandenplas, Y.. Knowledge of Flemish paediatricians about children's oral health - Results of a survey. *Acta Paediatrica, International Journal of Paediatrics.* 2008. 97:959-963	One or more exclusion criteria
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L1	Set, R.,Shastri, J.. Laboratory aspects of clinically significant rapidly growing mycobacteria. *Indian Journal of Medical Microbiology.* 2011. 29:343-352	One or more exclusion criteria

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L1	Lambertz, A.,Klink, C. D.,Röth, A.,Schmitz, D.,Pich, A.,Feher, K.,Bremus-Köbberling, E.,Neumann, U. P.,Junge, K.. Laser-induced drug release for local tumor control--a proof of concept. *J Surg Res.* 2014. 192:312-6	One or more exclusion criteria
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L1	Li, Y.,Wang, F.,Feng, J.,Lv, J. P.,Liu, Q.,Nan, F. R.,Zhang, W.,Qu, W. Y.,Xie, S. L.. Long term spatial-temporal dynamics of fluoride in sources of drinking	One or more exclusion criteria

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L1	Fu, H. Z.,Wang, M. H.,Ho, Y. S.. Mapping of drinking water research: A bibliometric analysis of research output during 1992-2011. *Science of the Total Environment.* 2013. 443:757-765	One or more exclusion criteria
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L1	Bongarzone, S.,Faugeras, V.,Sementa, T.,Gakpetor, C.,Gee, A. D.. Novel (18)F-labelled Metomidate analogues for targeting CYP11B2 beta hydroxylase - Towards a new PET radiotracer for managing personalised treatments for aldosteronoma-mediated hypertension. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2017. 60 (Supplement 1):S73	One or more exclusion criteria
L1	Yue, X.,Wang, Z.,Zhu, L.,Wang, Y.,Qian, C.,Ma, Y.,Kiesewetter, D. O.,Niu, G.,Chen, X.. Novel 19F activatable probe for the detection of matrix metalloprotease-2 activity by MRI/MRS. *Mol Pharm.* 2014. 11:4208-17	One or more exclusion criteria
L1	Nandy, S.,Roy, S.,Pawar, Y.,Ghosh, S.,Chaudhary, P. R.,Rajan, M. G. R.. Novel [18F]fluoroethylated thymidine derivative: Fully automated radiosynthesis and its evaluation as cellular proliferation imaging agent by PET. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2013. 1):S346	One or more exclusion criteria
L1	Chiotellis, A.,Sladojevich, F.,Mu, L.,Müller Herde, A.,Valverde, I. E.,Tolmachev, V.,Schibli, R.,Ametamey, S. M.,Mindt, T. L.. Novel chemoselective (18)F-radiolabeling of thiol-containing biomolecules under mild aqueous conditions. *Chem Commun (Camb).* 2016. 52:6083-6	One or more exclusion criteria

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L1	Papadopoulou, M. V.,Ji, M.,Bloomer, W. D.. Novel fluorinated hypoxia-targeted compounds as Non-invasive probes for measuring tumor-hypoxia by 19F-magnetic resonance spectroscopy (19F-MRS). *Anticancer Res.* 2006. 26:3253-8	One or more exclusion criteria
L1	Michelena, O.,Padro, D.,Carrillo-Carrión, C.,Del Pino, P.,Blanco, J.,Arnaiz, B.,Parak, W. J.,Carril, M.. Novel fluorinated ligands for gold nanoparticle labelling with applications in (19)F-MRI. *Chem Commun (Camb).* 2017. 53:2447-2450	One or more exclusion criteria
L1	Ashida, R.,Kawabata, K. I.,Asami, R.,Ioka, T.,Katayama, K.. Novel US/EUS guided site-specific treatment using ultrasonically activated superheated perfluorocarbon droplets. *Gastroenterology.* 2013. 1):S873	One or more exclusion criteria
L1	Litman, Y.,Pace, P.,Silva, L.,Hormigo, C.,Caro, R.,Gutierrez, H.,Bastianello, M.,Casale, G.. Novel, simple and fast automated synthesis of ¹⁸F-choline in a single module Synthera. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2013. 1):S454	One or more exclusion criteria

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L1	Crone, B. C.,Speth, T. F.,Wahman, D. G.,Smith, S. J.,Abulikemu, G.,Kleiner, E. J.,Pressman, J. G.. Occurrence of per- and polyfluoroalkyl substances (PFAS) in source water and their treatment in drinking water. *Critical Reviews in Environmental Science and Technology.* 2019. 49:2359-2396	One or more exclusion criteria
L1	Li, P.,Oyang, X.,Zhao, Y.,Tu, T.,Tian, X.,Li, L.,Zhao, Y.,Li, J.,Xiao, Z.. Occurrence of perfluorinated compounds in agricultural environment, vegetables, and fruits in regions influenced by a fluorine-chemical industrial park in China. *Chemosphere.* 2019. 225:659-667	One or more exclusion criteria
L1	Elfikrie, N.,Ho, Y. B.,Zaidon, S. Z.,Juahir, H.,Tan, E. S. S.. Occurrence of pesticides in surface water, pesticides removal efficiency in drinking water treatment plant and potential health risk to consumers in Tengi River Basin, Malaysia. *Science of the Total Environment.* 2020. 712 (no pagination):#pages#	One or more exclusion criteria

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L1	Mueller, D.,Klette, I.,Kalb, F.,Baum, R.. One pot synthesis of [18F]-Fluoroethylcholine. *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2010. 51:#pages#	One or more exclusion criteria
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L1	He, X.,Hai, L.,Su, J.,Wang, K.,Wu, X.. One-pot synthesis of sustained-released doxorubicin silica nanoparticles for aptamer targeted delivery to tumor cells. *Nanoscale.* 2011. 3:2936-42	One or more exclusion criteria
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L1	He, F.,Li, C.,Zhang, X.,Chen, Y.,Deng, X.,Liu, B.,Hou, Z.,Huang, S.,Jin, D.,Lin, J.. Optimization of upconversion luminescence of Nd(3+)-sensitized BaGdF5-based nanostructures and their application in dual-modality imaging and drug delivery. *Dalton Trans.* 2016. 45:1708-16	One or more exclusion criteria

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L1	Niu, Q.. Overview of the Relationship Between Aluminum Exposure and Health of Human Being. *Adv Exp Med Biol.* 2018. 1091:1-31	One or more exclusion criteria
L1	Khan, H.,Verma, Y.,Rana, S. V. S.. Oxidative stress induced by co-exposure to arsenic and fluoride in Wistar rat. *Cancer Medicine.* 2018. 7 (Supplement 1):33	One or more exclusion criteria
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L1	Staberg, M.,Norén, J. G.,Johnson, M.,Kopp, S.,Robertson, A.. Parental attitudes and experiences of dental care in children and adolescents with ADHD--a questionnaire study. *Swed Dent J.* 2014. 38:93-100	One or more exclusion criteria
L1	Loganathan, P.,Hedley, M. J.,Grace, N. D.. Pasture soils contaminated with fertilizer-derived cadmium and fluorine: livestock effects. *Rev Environ Contam Toxicol.* 2008. 192:29-66	One or more exclusion criteria
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L1	Badi, M. Y.,Azari, A.,Esrafili, A.,Ahmadi, E.,Gholami, M.. Performance evaluation of magnetized multiwall carbon nanotubes by iron oxide nanoparticles in removing fluoride from aqueous solution. [Persian]. *Journal of Mazandaran University of Medical Sciences.* 2015. 25:128-142	One or more exclusion criteria
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L1	Lin, H. H.,Lin, A. Y.. Photocatalytic oxidation of 5-fluorouracil and cyclophosphamide via UV/TiO2 in an aqueous environment. *Water Res.* 2014. 48:559-68	One or more exclusion criteria
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L1	Ding, L.,Yang, Q.,Yang, Y.,Ma, H.,Martin, J. D.. Potential risk assessment of groundwater to address the agricultural and domestic challenges in Ordos Basin. *Environmental Geochemistry & Health.* 2020. 03:03	One or more exclusion criteria
L1	Gai, Y.,Altine, B.,Han, N.,Lan, X.. Preclinical evaluation of a ¹⁸F-labeled phosphatidylinositol 3-kinase inhibitor for breast cancer imaging. *Journal of Nuclear Medicine. Conference.* 2019. 60:#pages#	One or more exclusion criteria
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L1	Dam, J.,Langkjaer, N.,Baun, C.,Olsen, B.. Preparation and evaluation of (18)F AlF-NOTA-NOC for PET imaging of neuroendocrine tumors. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S416-S417	One or more exclusion criteria
L1	Kong, Y.,Zhou, X.,Cao, G.,Xu, X.,Zou, M.,Qin, X.,Zhang, R.. Preparation of (99m)Tc-PQQ and preliminary biological evaluation for the NMDA receptor. *J Radioanal Nucl Chem.* 2011. 287:93-101	One or more exclusion criteria
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L1	Jarvis, H. G.,Heslop, P.,Kisima, J.,Gray, W. K.,Ndossi, G.,Maguire, A.,Walker, R. W.. Prevalence and aetiology of juvenile skeletal fluorosis in the south-west of the Hai district, Tanzania--a community-based prevalence and case-control study. *Trop Med Int Health.* 2013. 18:222-9	One or more exclusion criteria
L1	Isaac, A.,Silvia, W. D. C. R.,Somanna, S. N.,Mysorekar, V.,Narayana, K.,Srikantaiah, P.. Prevalence and manifestations of water-born fluorosis among schoolchildren in Kaiwara village of India: A preliminary study. *Asian Biomedicine.* 2009. 3:563-566	One or more exclusion criteria
L1	Carvalho, T. S.,Kehrle, H. M.,Sampaio, F. C.. Prevalence and severity of dental fluorosis among students from João Pessoa, PB, Brazil. *Braz Oral Res.* 2007. 21:198-203	One or more exclusion criteria
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L1	Beltrán-Aguilar, E. D.,Barker, L.,Dye, B. A.. Prevalence and severity of dental fluorosis in the United States, 1999-2004. *NCHS Data Brief.* 2010. #volume#:1-8	One or more exclusion criteria

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L1	Karthikeyan, K.,Nanthakumar, K.,Velmurugan, P.,Tamilarasi, S.,Lakshmanaperumalsamy, P.. Prevalence of certain inorganic constituents in groundwater samples of Erode district, Tamilnadu, India, with special emphasis on fluoride, fluorosis and its remedial measures. *Environmental Monitoring and Assessment.* 2010. 160:141-155	One or more exclusion criteria
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L1	Veiga, N.,Amaral, O.,Pereira, C.,Ribeiro, C.,Arrimar, A.,Coelho, I.. Prevalence of dental caries and fluorosis among a sample of adolescents living in a fluoridated and a non-fluoridated water region. *European Journal of Epidemiology.* 2013. 1):S226	One or more exclusion criteria
L1	Xia, Y.,Li, B. L.,Zhao, X. H.,Huang, Y. X.,Chen, J. K.,Chen, S. H.,Ou, H. Z.,Chen, S. X.. Prevalence of dental caries in Shantou City Guangdong Province fluorosis areas after water improvement. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:309-311	One or more exclusion criteria

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L1	Punitha, V. C.,Sivaprakasam, P.,Elango, R.,Balasubramanian, R.,Midhun Kumar, G. H.,Sudhir Ben Nelson, B. T.. Prevalence of dental fluorosis in a non-endemic district of Tamil Nadu, India. *Biosciences Biotechnology Research Asia.* 2014. 11:159-163	One or more exclusion criteria
L1	Casanova-Rosado, A. J.,Medina-Sols, C. E.,Casanova-Rosado, J. F.,Vallejos-Sanchez, A. A.,de la Rosa-Santillana, R.,Mendoza-Rodriguez, M.,Villalobos-Rodelo, J. J.,Maupome, G.. Prevalence of dental fluorosis in eight cohorts of Mexicans born in the establishment of the national domestic salt fluoridation. *Gaceta Medica de Mexico.* 2013. 149:27-35	One or more exclusion criteria

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L1	Sharma, J. D.,Sohu, D.,Jain, P.. Prevalence of neurological manifestations in a human population exposed to fluoride in drinking water. *Fluoride.* 2009. 42:127-132	One or more exclusion criteria
L1	John, J.,Hariharan, M.,Remy, V.,Haleem, S.,Thajuraj, P. K.,Deepak, B.,Rajeev, K. G.,Devang Divakar, D.. Prevalence of skeletal fluorosis in fisherman from Kutch coast, Gujarat, India. *Rocz Panstw Zakl Hig.* 2015. 66:379-82	One or more exclusion criteria
L1	Syme, S. L.. Preventing disease and promoting health: The need for some new thinking. *Sozial- und Praventivmedizin.* 2006. 51:247-248	One or more exclusion criteria
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L1	Mei, M. L.,Ito, L.,Chu, C. H.,Lo, E. C. M.,Zhang, C. F.. Prevention of dentine caries using silver diamine fluoride application followed by Er:YAG laser irradiation: an in vitro study. *Lasers in Medical Science.* 2014. 29:1785-1791	One or more exclusion criteria
L1	Korner, P.,Wiedemeier, D. B.,Attin, T.,Wegehaupt, F. J.. Prevention of Enamel Softening by Rinsing with a Calcium Solution before Dental Erosion. *Caries research.* 2020. #volume#:1-7	One or more exclusion criteria
L1	Zhang, L.,Huang, D.,Yang, J.,Wei, X.,Qin, J.,Ou, S.,Zhang, Z.,Zou, Y.. Probabilistic risk assessment of Chinese residents' exposure to fluoride in improved drinking water in endemic fluorosis areas. *Environmental Pollution.* 2017. 222:118-125	One or more exclusion criteria
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L1	Bruton, T. A.,Blum, A.. Proposal for coordinated health research in PFAS-contaminated communities in the United States. *Environmental Health: A Global Access Science Source.* 2017. 16 (1) (no pagination):#pages#	One or more exclusion criteria
L1	Wilhelm-Buchstab, T.,Thelen, C.,Leitzen, C.,Schmeel, L. C.,Mudder, T.,Oberste-Beulmann, S.,Schuller, H.,Rohner, F.,Garbe, S.,Schoroth,	One or more exclusion criteria

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L1	Berry, C.. Public health impact of food: Quantity, quality, supplements and appetites. *Toxicology Letters.* 2013. 1):S2	One or more exclusion criteria
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L1	Hayat, E.,Baba, A.. Quality of groundwater resources in Afghanistan. *Environmental Monitoring and Assessment.* 2017. 189 (7) (no pagination):#pages#	One or more exclusion criteria
L1	Tomlinson, R. E.,Silva, M. J.,Shoghi, K. I.. Quantification of skeletal blood flow and fluoride metabolism in rats using PET in a pre-clinical stress fracture model. *Mol Imaging Biol.* 2012. 14:348-54	One or more exclusion criteria

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L1	Klomp, D.,van Laarhoven, H.,Scheenen, T.,Kamm, Y.,Heerschap, A.. Quantitative 19F MR spectroscopy at 3 T to detect heterogeneous capecitabine metabolism in human liver. *NMR in Biomedicine.* 2007. 20:485-92	One or more exclusion criteria
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L1	Levine, K. E.,Redmon, J. H.,Elledge, M. F.,Wanigasuriya, K. P.,Smith, K.,Munoz, B.,Waduge, V. A.,Periris-John, R. J.,Sathiakumar, N.,Harrington, J.	One or more exclusion criteria

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L1	Lee, S. H.,Park, J. K.,Lee, S. Y.,Lee, J.,Ido, T.. Radiolabeling of SUV size liposome with hexadecyl-4-[¹⁸F]fluorobenzoate ([¹⁸F] HFB) for tumor imaging. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S373-S374	One or more exclusion criteria
L1	Helin, S.,Kirjavainen, A.,Arponen, E.,Forsback, S.,Marjamaki, P.,Haaparanta-Solin, M.,Bender, D.,Peters, D.,Solin, O.. Radiolabelling of the norepinephrine transporter ligand [^{11C}]NS8880 and its evaluation in the rat. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2013. 1):S103	One or more exclusion criteria
L1	Ozerskaya, A.,Belugin, K.,Tokarev, N.,Chanchikova, N.,Larkina, M.,Podrezova, E.,Yusubov, M.,Belousov, M.. Radiopharmaceutical production technology at the Nuclear Medicine Centre Federal Siberian Research Clinical Centre, Russia. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2019. 62 (Supplement 1):S577	One or more exclusion criteria

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L1	Graf, K.,Hellman, M.,Kavathas, S.,Dewey, S.,Schiffer, W.,Subramaniam, G.,Chaly, T.. Radiosynthesis and in vivo evaluation of [¹⁸F]C8-ceramide analogues as potential tumor imaging agents. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2011. 1):S202	One or more exclusion criteria
L1	Yamamoto, F.,Yamahara, R.,Makino, A.,Kurihara, K.,Tsukada, H.,Hara, E.,Hara, I.,Kizaka-Kondoh, S.,Ohkubo, Y.,Ozeki, E.,Kimura, S.. Radiosynthesis and initial evaluation of (18)F labeled nanocarrier composed of poly(L-lactic acid)-block-poly(sarcosine) amphiphilic polydepsipeptide. *Nucl Med Biol.* 2013. 40:387-94	One or more exclusion criteria
L1	Honda, N.,Yoshimoto, M.,Mizukawa, Y.,Osaki, K.,Kanai, Y.,Kurihara, H.,Tateishi, H.,Takahashi, K.. Radiosynthesis of 2-[¹⁸F]fluoro-4-borono-phenylaranine ([¹⁸F]FBPA) using copper mediated oxidative aromatic nucleophilic [¹⁸F]fluorination. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2017. 60 (Supplement 1):S512	One or more exclusion criteria

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L1	Malik, N.,Zlatopolskiy, B.,Voelter, W.,Solbach, C.,Machulla, H. J.,Reske, S. N.. Radiosynthesis of a new PSMA targeting ligand ([¹⁸F]FPy-DUPA-Pep). *NuklearMedizin.* 2011. 50 (2):A117-A118	One or more exclusion criteria
L1	Park, J. Y.,Son, J.,Yun, M.,Chun, J. H.. Radiosynthesis of mGlu5 PET tracer [¹⁸F]PSS232 with protic solvent additives. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2017. 60 (Supplement 1):S289	One or more exclusion criteria
L1	Turkman, N.,Gelovani, J. G.,Alauddin, M.. Radiosynthesis of N5-[¹⁸F]fluoroacetylornithine (N5-[¹⁸F]FAO) for PET imaging of ornithine decarboxylase (ODC). *Molecular Imaging and Biology.* 2010. 2):S929	One or more exclusion criteria
L1	Baguet, T.,Verhoeven, J.,De Lombaerde, S.,Piron, S.,Descamps, B.,Vanhove, C.,Beyzavi, H.,De Vos, F.. Radiosynthesis, in vitro and in vivo evaluation of [¹⁸F]Fluorphenylglutamine and [¹⁸F]Fluorbiphenylglutamine as novel ASCT-2 directed tumor	One or more exclusion criteria

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L1	Old, O. J.,Isabelle, M.,Lloyd, G.,Kendall, C.,Barr, H.,Stone, N.. Raman mapping for pathology classification: The need for speed. *Gut.* 2015. 1):A485-A486	One or more exclusion criteria
L1	Kirsch, M.,Schackert, G.,Salzer, R.,Krafft, C.. Raman spectroscopic imaging for in vivo detection of cerebral brain metastases. *Anal Bioanal Chem.* 2010. 398:1707-13	One or more exclusion criteria
L1	Barr, H.,Isabelle, M.,Old, O.,Lloyd, G.,Lau, K.,Dorney, J.,Lewis, A.,Geraint, T.,Shepherd, N.,Bell, I.,Stone, N.,Kendall, C.. Raman spectroscopycancer diagnostic for pathology of barrett's oesophagus. *Gut.* 2016. 65 (Supplement 1):A177	One or more exclusion criteria
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L1	Lisova, K.,Chen, B. Y.,Wang, J.,Fong, K. M.,Clark, P. M.,van Dam, R. M.. Rapid, efficient, and economical synthesis of PET tracers in a droplet microreactor: application to O-(2-[(18)F]fluoroethyl)-L-tyrosine ([(18)F]FET). *EJNMMI Radiopharm Chem.* 2019. 5:1	One or more exclusion criteria
L1	Family, L.,Zheng, G.,Cabezas, M.,Cloud, J.,Hsu, S.,Rubin, E.,Smith, L. V.,Kuo, T.. Reasons why low-income people in urban areas do not drink tap water. *J Am Dent Assoc.* 2019. 150:503-513	One or more exclusion criteria
L1	Craig, L.,Lutz, A.,Berry, K. A.,Yang, W.. Recommendations for fluoride limits in drinking water based on estimated daily fluoride intake in the Upper East Region, Ghana. *Science of the Total Environment.* 2015. 532:127-37	One or more exclusion criteria
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L1	Indermitte, E.,Saava, A.,Karro, E.. Reducing exposure to high fluoride drinking water in Estonia-a countrywide study. *International Journal of Environmental Research & Public Health [Electronic Resource].* 2014. 11:3132-42	One or more exclusion criteria
L1	Cherng, A. M.,Takagi, S.,Chow, L.. Reduction in dentin permeability using a slurry containing dicalcium phosphate and calcium hydroxide. *Journal of Biomedical Materials Research - Part B Applied Biomaterials.* 2006. 78:291-MA	One or more exclusion criteria
L1	Manne, M.,Validandi, V.,Khandare, A. L.. Reduction of fluoride toxicity by tamarind components: An in silico study. *Fluoride.* 2018. 51:122-136	One or more exclusion criteria
L1	Mandinic, Z.,Curcic, M.,Antonijevic, B.,Carevic, M.. Relationship between dental fluorosis and fluoride content in hair of schoolchildren from fluorotic and non-fluorotic regions in Serbia. *Toxicology Letters.* 2009. 1):S236	One or more exclusion criteria
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L1	Yang, C. C.,Li, B. L.,Zhao, X. H.,Huang, Y. X.,Chen, J. K.,Chen, S. H.,Zhang, G. S.,Ou, H. H.,Chen, S. X.. Relationship between urinary fluoride level, incidences of dental fluorosis and caries of children in fluorosis areas after change of water sources. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:673-676	One or more exclusion criteria
L1	Xiang, Q.,Zhou, M.,Wu, M.,Zhou, X.,Lin, L.,Huang, J.,Liang, Y.. Relationships between daily total fluoride intake and dental fluorosis and dental caries. *Journal of Nanjing Medical University.* 2009. 23:33-39	One or more exclusion criteria
L1	de Vries, A.,Moonen, R.,Yildirim, M.,Langereis, S.,Lamerichs, R.,Pikkemaat, J. A.,Baroni, S.,Terreno, E.,Nicolay, K.,Strijkers, G. J.,Grull, H.. Relaxometric studies of gadolinium-functionalized perfluorocarbon nanoparticles for MR imaging. *Contrast Media and Molecular Imaging.* 2014. 9:83-91	One or more exclusion criteria
L1	Mirhashemi, A. H.,Jahangiri, S.,Kharrazifard, M. J.. Release of nickel and chromium ions from orthodontic wires following the use of teeth whitening mouthwashes. *Progress in Orthodontics.* 2018. 19 (1) (no pagination):#pages#	One or more exclusion criteria
L1	Shen, J.,Schafer, A.. Removal of fluoride and uranium by nanofiltration and reverse osmosis: A review. *Chemosphere.* 2014. 117:679-691	One or more exclusion criteria

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L1	Whelan, E. M.. Reply. *MedGenMed Medscape General Medicine.* 2008. 10 (4) (no pagination):#pages#	One or more exclusion criteria
L1	Sun, D.. Report on the surveillance of endemic fluorosis of drinking water type in China in 2005 and 2006. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:175-180	One or more exclusion criteria
L1	Wei, S. Y.,Ding, P.,Ding, S. R.,Zhang, H. Y.,Li, S. B.,Zhang, X. L.,Chen, W. G.,Lu, A.,Li, Y. F.. Report on the surveillance results of endemic fluorosis in Qinghai Province in 2007. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:671-672	One or more exclusion criteria
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L1	Frood, R.,McDermott, G.,Scarsbrook, A.. Respiratory-gated PET/CT for pulmonary lesion characterisation-promises and problems. *Br J Radiol.* 2018. 91:20170640	One or more exclusion criteria
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L1	Guissouma, W.,Hakami, O.,Al-Rajab, A. J.,Tarhouni, J.. Risk assessment of fluoride exposure in drinking water of Tunisia. *Chemosphere.* 2017. 177:102-108	One or more exclusion criteria
L1	Waugh, D. T.,Potter, W.,Limeback, H.,Godfrey, M.. Risk assessment of fluoride intake from tea in the republic of ireland and its implications for public health and water fluoridation. *International Journal of Environmental Research and Public Health.* 2016. 13 (3) (no pagination):#pages#	One or more exclusion criteria

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L1	Soloviev, D.,Lewis, D. Y.,Ros, S.,Hu, D. E.,D'Santos, P.,Brindle, K. M.. Simplified synthesis of [18F]tetrafluoroborate for NIS reporter imaging by PET. *Molecular Imaging and Biology.* 2016. 18 (2 Supplement):S1197-S1198	One or more exclusion criteria
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L1	Ingallinella, A. M.,Pacini, V. A.,Fernandez, R. G.,Vidoni, R. M.,Sanguinetti, G.. Simultaneous removal of arsenic and fluoride from groundwater by	One or more exclusion criteria

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L1	Bajpai, A.,Lakshminarayanan, N.,Khushwaha, K.,Banerjee, S.. Simultaneous synthesis of O-(2'-[¹⁸F] fluoroethyltyrosine and [¹⁸F] fluoromisonidazole using solid phase extraction method. *Indian Journal of Nuclear Medicine.* 2017. 32 (5 Supplement 1):S15	One or more exclusion criteria
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L1	Izuora, K.,Twombly, J. G.,Whitford, G. M.,Demertzis, J.,Pacifici, R.,Whyte, M. P.. Skeletal fluorosis from brewed tea. *J Clin Endocrinol Metab.* 2011. 96:2318-24	One or more exclusion criteria

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L1	Sato, M.,Hanmoto, T.,Yachiguchi, K.,Tabuchi, Y.,Kondo, T.,Endo, M.,Kitani, Y.,Sekiguchi, T.,Urata, M.,Hai, T. N.,Srivastav, A. K.,Mishima, H.,Hattori, A.,Suzuki, N.. Sodium fluoride induces hypercalcemia resulting from the upregulation of both osteoblastic and osteoclastic activities in goldfish, Carassius auratus. *Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology.* 2016. 189:54-60	One or more exclusion criteria

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L1	Kumar, R.,Mittal, S.,Sahoo, P. K.,Sahoo, S. K.. Source apportionment, chemometric pattern recognition and health risk assessment of groundwater from southwestern Punjab, India. *Environ Geochem Health.* 2020. #volume#:#pages#	One or more exclusion criteria
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L1	Chowdhury, C. R.,Shahnawaz, K.,Kumari, D.,Chowdhury, A.,Bedi, R.,Lynch, E.,Harding, S.,Grootveld, M.. Spatial distribution mapping of drinking water fluoride levels in Karnataka, India: fluoride-related health effects. *Perspectives in Public Health.* 2016. 136:353-360	One or more exclusion criteria
L1	Zhang, L.,Zhao, L.,Zeng, Q.,Fu, G.,Feng, B.,Lin, X.,Liu, Z.,Wang, Y.,Hou, C.. Spatial distribution of fluoride in drinking water and health risk assessment of children in typical fluorosis areas in north China. *Chemosphere.* 2020. 239:124811	One or more exclusion criteria
L1	Ranasinghe, N.,Kruger, E.,Tennant, M.. Spatial distribution of groundwater fluoride levels and population at risk for dental caries and dental fluorosis in Sri Lanka. *Int Dent J.* 2019. 69:295-302	One or more exclusion criteria
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L1	Shashi, A.,Bhardwaj, M.. Study on blood biochemical diagnostic indices for hepatic function biomarkers in endemic skeletal fluorosis. *Biol Trace Elem Res.* 2011. 143:803-14	One or more exclusion criteria

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L1	Attia, K.,Visser, T.,Steven, J.,Slart, R.,Antunes, I.,Van Der Hoek, S.,Elsinga, P.,Heerspink, H.. Synthesis and evaluation of [¹⁸F] canagliflozin	One or more exclusion criteria

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L1	Kumar, P.,Sun, W.,Wuest, M.,Knaus, E. E.,Wiebe, L. I.. Synthesis and initial in vitro and in vivo evaluation of 2'-[¹⁸F]Fluoro-2'-deoxythymidine	One or more exclusion criteria

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L1	Akula, M. R.,Blevins, D. W.,Kabalka, G. W.,Osborne, D.. Synthesis of N-[4-(2'-[¹⁸F]fluoroethyloxybenzoyl)]pyrrolidin-2-one, a potential new brain imaging agent. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2015. 1):S214	One or more exclusion criteria
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L1	Tanpure, R. P.,George, C. S.,Strecker, T. E.,Devkota, L.,Tidmore, J. K.,Lin, C. M.,Herdman, C. A.,Macdonough, M. T.,Sriram, M.,Chaplin, D. J.,Trawick, M. L.,Pinney, K. G.. Synthesis of structurally diverse benzosuberene analogues and their biological evaluation as anti-cancer agents. *Bioorg Med Chem.* 2013. 21:8019-32	One or more exclusion criteria
L1	Martić, M.,Pernot, L.,Westermaier, Y.,Perozzo, R.,Kraljević, T. G.,Krištafor, S.,Raić-Malić, S.,Scapozza, L.,Ametamey, S.. Synthesis, crystal structure, and in vitro biological evaluation of C-6 pyrimidine derivatives: new lead structures for monitoring gene expression in vivo. *Nucleosides Nucleotides Nucleic Acids.* 2011. 30:293-315	One or more exclusion criteria
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L1	Boyles, A. L.,Blain, R. B.,Rochester, J. R.,Avanasi, R.,Goldhaber, S. B.,McComb, S.,Holmgren, S. D.,Masten, S. A.,Thayer, K. A.. Systematic review of community health impacts of mountaintop removal mining. *Environment International.* 2017. 107:163-172	One or more exclusion criteria
L1	Czajka, M.. Systemic effects of fluoridation. *Journal of Orthomolecular Medicine.* 2012. 27:123-130	One or more exclusion criteria
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L1	Sikorska-Jaroszynska, M. H. J.,Mielnik-Blaszczak, M.,Krawczyk, D.,Wrobel, R.,Blaszczak, J.. Tea - Natural source of fluoride compounds. *Annales Universitatis Mariae Curie-Sklodowska, Sectio DDD: Pharmacia.* 2012. 25:247-249	One or more exclusion criteria
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L1	Skillman, S. M.,Doescher, M. P.,Mouradian, W. E.,Brunson, D. K.. The challenge to delivering oral health services in rural America. *Journal of Public Health Dentistry.* 2010. 70 Suppl 1:S49-57	One or more exclusion criteria
L1	Mirzabeygi Rad Fard, M.,Yousefi, M.,Soleimani, H.,Mohammadi, A. A.,Mahvi, A. H.,Abbasnia, A.,Wasana, H. M.,Perera, G. D.,De Gunawardena, P. S.,Bandara, J.. The The impact of aluminum, fluoride, and aluminum-fluoride complexes in drinking water on chronic kidney disease. Data Brief. 2018. 18:40-46 concentration data of fluoride and health risk assessment in drinking water in the Ardakan city of Yazd province, Iran	One or more exclusion criteria
L1	Genovesi, A.,Sachero, E.,Lorenzi, C.. The dental hygienist's role in the laser treatment of the dentine hipersensitivity. [Italian]. *Prevenzione e Assistenza Dentale.* 2010. 36:32-35	One or more exclusion criteria
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L1	Liu, Y.,Sun, J.,Li, B.,Liu, X.,Li, M.,Cui, J.,Liu, H.,Sun, Z.,Li, Y.,Wu, J.,Zhang, W.,Gao, Y.. The differences of brick-tea fluorosis of four ethnic in China. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:315-319	One or more exclusion criteria
L1	Lu, Q.,He, D.,Yang, P.,Li, S.,Jiang, H.,Chen, P.,Pa, G.,Wu, H.,La, C.,Wei, S.. The distribution of drinking-tea-borne fluorosis in the six ethnics in Qinghai Province. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:404-406	One or more exclusion criteria
L1	Tirapelli, C.,Panzeri, H.,Lara, E. H.,Soares, R. G.,Peitl, O.,Zanotto, E. D.. The effect of a novel crystallised bioactive glass-ceramic powder on dentine hypersensitivity: a long-term clinical study. *J Oral Rehabil.* 2011. 38:253-62	One or more exclusion criteria
L1	Lyaruu, D. M.,Bronckers, A. L. J. J.,Santos, F.,Mathias, R.,DenBesten, P.. The effect of fluoride on enamel and dentin formation in the uremic rat incisor. *Pediatric Nephrology.* 2008. 23:1973-1979	One or more exclusion criteria

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L1	Crocombe, L. A.,Brennan, D. S.,Slade, G. D.,Stewart, J. F.,Spencer, A. J.. The effect of lifetime fluoridation exposure on dental caries experience of younger rural adults. *Aust Dent J.* 2015. 60:30-7	One or more exclusion criteria
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L1	Shim, M. Y.,Parr, C.,Pesti, G. M.. The effects of dietary fluoride on growth and bone mineralization in broiler chicks. *Poult Sci.* 2011. 90:1967-74	One or more exclusion criteria
L1	Mendoza-Schulz, A.,Solano-Agama, C.,Arreola-Mendoza, L.,Reyes-Marquez, B.,Barbier, O.,Del Razo, L. M.,Mendoza-Garrido, M. E.. The effects of fluoride on cell migration, cell proliferation, and cell metabolism in GH4C1 pituitary tumour cells. *Toxicology Letters.* 2009. 190:179-86	One or more exclusion criteria

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L1	Kim, S. Y.,Kim, E. J.,Kim, D. S.,Lee, I. B.. The evaluation of dentinal tubule occlusion by desensitizing agents: a real-time measurement of dentinal fluid flow rate and scanning electron microscopy. *Oper Dent.* 2013. 38:419-28	One or more exclusion criteria
L1	Xu, G. Y.,Li, J. X.,Hua, J. L.. The evaluation report for restoration and reconstruction of endemic disease prevention needed in areas severely hit by the earthquake in Shaanxi province. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:295-298	One or more exclusion criteria
L1	Mel'Nichuk, L. P.,Khodasevich, L. S.. The external application of "Plastunskaya" fluoride-containing mineral water in the course of the combined spa and health resort-based treatment of deforming osteoarthrosis. [Russian]. *Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury.* 2015. 92:48-50	One or more exclusion criteria
L1	Al-Jiboury, H.,Wilgus, J.,Benhammou, J.,Patel, A.,Jacob, N.,Ohning, G.,Otomo-Corgel, J.,Pisegna, J. R.. The gastric refluxate in patients with gastroesophageal reflux disease (GERD) has a protective effect on periodontal microbiota. *American Journal of Gastroenterology.* 2015. 1):S731	One or more exclusion criteria
L1	Foth, M.. The increasing relevance of public health research in the last 95 years. *Journal of Public Health (Germany).* 2012. 20:209-211	One or more exclusion criteria

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L1	Esteves-Oliveira, M.,Zezell, D. M.,Velloso, W. F.,Meister, J.,Franzen, R.,Lampert, F.,Eduardo, C. P.,Apel, C.. The influence of pulse duration and irradiation time of a CO2 laser on enamel caries resistance. *Lasers in Medical Science.* 2009. 24 (3):496	One or more exclusion criteria
L1	Huang, D. Y.,Zhang, X. H.,Pu, Y.,Yu, M. J.. The intervention effects of soybean, selenium powder, spiral algae on rats of fluoride poisoning with high aluminum. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:376-380	One or more exclusion criteria
L1	Jia, L. H.,Ma, J.,Du, Y. G.,Ma, D. R.,Yao, G. J.,Liang, S. L.,Zhang, J. Q.,Chong, Z. S.,Zhao, J.,Xu, D.. The investigation of drinking-water-borne endemic fluorosis in Hebei province in 2009. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:184-187	One or more exclusion criteria
L1	Chachra, D.,Limeback, H.,Willett, T. L.,Grynpas, M. D.. The long-term effects of water fluoridation on the human skeleton. *J Dent Res.* 2010. 89:1219-23	One or more exclusion criteria

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L1	Petrova, A.,Ol'shevskaya, V.,Zaitsev, A.,Tatarskiy, V.,Radchenko, A.,Kostyukov, A.,Kalinina, E.,Kuzmin, V.,Miyoshi, N.,Shtil, A.. The novel tetracarboranylchlorin derivative for binary anticancer treatment: rapid tumor elimination via superoxide anion production. *FEBS Open Bio.* 2019. 9 (Supplement 1):334-335	One or more exclusion criteria
L1	Bharatwaj, B.,Wu, L.,Whittum-Hudson, J. A.,da Rocha, S. R.. The potential for the noninvasive delivery of polymeric nanocarriers using propellant-based inhalers in the treatment of Chlamydial respiratory infections. *Biomaterials.* 2010. 31:7376-85	One or more exclusion criteria
L1	Jarvis, H. G.,Heslop, P. S.,Kissima, J.,Walker, R.. The prevalence and characteristics of fluorosis causing skeletal deformities in rural Tanzania. *Arthritis and Rheumatism.* 2010. 10):1568	One or more exclusion criteria
L1	Akosu, T. J.,Zoakah, A. I.,Chirdan, O. A.. The prevalence and severity of dental fluorosis in the high and low altitude parts of Central Plateau, Nigeria. *Community Dent Health.* 2009. 26:138-42	One or more exclusion criteria
L1	Alavi, A. A.,Amirhakimi, E.,Karami, B.. The prevalence of dental caries in 5 - 18-year-old insulin-dependent diabetics of Fars Province, southern Iran. *Arch Iran Med.* 2006. 9:254-60	One or more exclusion criteria
L1	Zhao, H.,Zhang, H.,Cui, P.,Ding, F.,Wang, G.,Li, R.,Jenks, M. A.,Lu, S.,Xiong, L.. The Putative E3 Ubiquitin Ligase ECERIFERUM9 Regulates Abscisic Acid	One or more exclusion criteria

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L1	Mustafa, D. E.,Younis, U. M.,Elhag, S. A. A.. The relationship between the fluoride levels in drinking water and the schooling performance of children in rural areas of Khartoum state, Sudan. *Fluoride.* 2018. 51:102-113	One or more exclusion criteria
L1	Ding, Y.,YanhuiGao,,Sun, H.,Han, H.,Wang, W.,Ji, X.,Liu, X.,Sun, D.. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. *Journal of Hazardous Materials.* 2011. 186:1942-1946	One or more exclusion criteria
L1	Arpaia, D.,Montuori, P.,Ciancia, G.,Ippolito, S.,Ferraro, A.,Galante, F.,Lombardi, G.,Pettinato, G.,Triassi, M.,Biondi, B.. The risk of thyroid cancer related to the vesuvius in the region of Campania, Italy. *European Thyroid Journal.* 2011. Conference Publication: (var.pagings).:140-141	One or more exclusion criteria
L1	Gooch, B. F.,Griffin, S. O.,Malvitz, D. M.. The role of evidence in formulating public health programs to prevent oral disease and promote oral health in the United States. *J Evid Based Dent Pract.* 2006. 6:85-9	One or more exclusion criteria
L1	Pollick, H.. The Role of Fluoride in the Prevention of Tooth Decay. *Pediatric Clinics of North America.* 2018. 65:923-940	One or more exclusion criteria
L1	Wimalawansa, S. J.. The role of ions, heavy metals, fluoride, and agrochemicals: critical evaluation of potential aetiological factors of chronic	One or more exclusion criteria

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L1	Shcaira, V.,Gambareli, F.,Correa, M. E.,Moraes, P.. The role of mouth disease diagnosis in the context of the Brazilian health system. A 19 years retrospective study in Cosmopolis city with emphasis in oral cancer. *Supportive Care in Cancer.* 2010. 3):S141	One or more exclusion criteria
L1	Chiu, R. S.,Nahal, H.,Provart, N. J.,Gazzarrini, S.. The role of the Arabidopsis FUSCA3 transcription factor during inhibition of seed germination at high temperature. *BMC Plant Biol.* 2012. 12:15	One or more exclusion criteria
L1	Li, Z.,Zhang, H.,Zhao, C.,Li, Y.,Chen, B.. The situation of brick tea type fluorosis in inner mongolia in 2009 and 2012. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:530-533	One or more exclusion criteria
L1	Pepper, I. L.. The soil health-human health nexus. *Critical Reviews in Environmental Science and Technology.* 2013. 43:2617-2652	One or more exclusion criteria
L1	Stafford, R.. The spin-echo sequence; K-space. *Medical Physics.* 2017. 44 (6):3094	One or more exclusion criteria

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L1	Shen, Z.,Ning, L.,Wu, R.,Brindle, K.. The technique methods and progress of MR pH imaging. *Neuroradiology Journal.* 2010. 1):304	One or more exclusion criteria
L1	Whelan, E. M.. The top ten unfounded health scares of the year. *MedGenMed Medscape General Medicine.* 2008. 10 (2) (no pagination):#pages#	One or more exclusion criteria
L1	Kanduti, D.,Sterbenk, P.,Artnik, B.. The use of fluoride and its effect on health. [Slovene]. *Zdravniski Vestnik.* 2016. 85:348-353	One or more exclusion criteria
L1	Yu, S.,Zhang, W.,Hao, F.,Zhang, L.. Therapeutic mechanism of shen qi fu zheng zhu she ye toward the adrenal cortex ultrastructure in cancer-related fatigue. [Chinese]. *Chinese Journal of Clinical Oncology.* 2013. 40:621-624+633	One or more exclusion criteria
L1	Tailor, R.,Tolani, N.,Ibbott, G. S.. Thermoluminescence dosimetry measurements of brachytherapy sources in liquid water. *Med Phys.* 2008. 35:4063-9	One or more exclusion criteria
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L1	Yu, X.,Chen, J.,Li, Y.,Liu, H.,Hou, C.,Zeng, Q.,Cui, Y.,Zhao, L.,Li, P.,Zhou, Z.,Pang, S.,Tang, S.,Tian, K.,Zhao, Q.,Dong, L.,Xu, C.,Zhang, X.,Zhang, S.,Liu, L.,Wang, A.. Threshold effects of moderately excessive fluoride exposure on children's health: A potential association between dental fluorosis	One or more exclusion criteria

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L1	Yang, K.,Yang, X.,Zhao, X.,Lamy de la Chapelle, M.,Fu, W.. THz Spectroscopy for a Rapid and Label-Free Cell Viability Assay in a Microfluidic Chip Based on an Optical Clearing Agent. *Anal Chem.* 2019. 91:785-791	One or more exclusion criteria
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L1	Holmström, K. E.,Berger, U.. Tissue distribution of perfluorinated surfactants in common guillemot (Uria aalge) from the Baltic Sea. *Environ Sci Technol.* 2008. 42:5879-84	One or more exclusion criteria
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L1	Gore, F.,Fawell, J.,Bartram, J.. Too much or too little? A review of the conundrum of selenium. *Journal of Water & Health.* 2010. 8:405-16	One or more exclusion criteria
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L1	Aurlene, N.,Manipal, S.,Rajmohan,,Prabu, D.,Sindhu, R.. Topical fluoride as a panacea for dental caries: A review. *Journal of Pharmaceutical Sciences and Research.* 2019. 11:3320-3325	One or more exclusion criteria
L1	Machado, I.,Buhl, V.,Manay, N.. Total arsenic and inorganic arsenic speciation in groundwater intended for human consumption in Uruguay: Correlation with	One or more exclusion criteria

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L1	Paiste, M.,Levine, M.,Bono, J. V.. Total knee arthroplasty in a patient with skeletal fluorosis. *Orthopedics.* 2012. 35:e1664-7	One or more exclusion criteria
L1	McCready, R.,Dizdarevic, S.. Towards improving the sensitivity of ¹⁸F bone imaging. *Nuclear Medicine Communications.* 2014. 35 (5):554	One or more exclusion criteria
L1	Johnson, C. A.,Berg, M.,Sabatini, D.. Towards sustainable safe drinking water supply in low- and middle-income countries: The challenges of geogenic contaminants and mitigation measures. *Science of the Total Environment.* 2014. 488-489:475-476	One or more exclusion criteria
L1	Steen, J.,Denk, C.,Norregaard, K.,Jorgensen, J.,Rossin, R.,Svatunek, D.,Edem, P.,Robillard, M.,Kjaer, A.,Kristensen, J.,Mikula, H.,Herth, M.. Towards the dual click ¹⁸F-labeling of Antibodies. *Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.* 2018. 59:#pages#	One or more exclusion criteria

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L1	Grandjean, P.,Herz, K. T.. Trace elements as paradigms of developmental neurotoxicants: Lead, methylmercury and arsenic. *#journal#.* 2015. 31:#pages#	One or more exclusion criteria
L1	Frezzo, J. A.,Hoang, D. M.,Wadghiri, Y. Z.,Montclare, J. K.. Traceable and thermoresponsive multifunctional engineered protein drug delivery agents for metastatic breast cancer. *Molecular Imaging and Biology.* 2016. 18 (2 Supplement):S279	One or more exclusion criteria
L1	Wickramarathna, S.,Balasooriya, S.,Diyabalanage, S.,Chandrajith, R.. Tracing environmental aetiological factors of chronic kidney diseases in the dry zone of Sri Lanka-A hydrogeochemical and isotope approach. *J Trace Elem Med Biol.* 2017. 44:298-306	One or more exclusion criteria
L1	Janka, Z.. Tracing trace elements in mental functions. [Hungarian]. *Ideggyogyaszati Szemle.* 2019. 72:367-379	One or more exclusion criteria
L1	Kislukhin, A. A.,Xu, H.,Adams, S. R.,Narsinh, K.,Tsien, R. Y.,Ahrens, E. T.. Tracking transplanted cells with paramagnetic fluorinated nanoemulsions.	One or more exclusion criteria

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L1	Sikora, B.,Fronc, K.,Kaminska, I.,Koper, K.,Szewczyk, S.,Paterczyk, B.,Wojciechowski, T.,Sobczak, K.,Minikayev, R.,Paszkowicz, W.,Stepien, P.,Elbaum, D.. Transport of NaYF4:Er3+, Yb3+ up-converting nanoparticles into HeLa cells. *Nanotechnology.* 2013. 24:235702	One or more exclusion criteria
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L1	Farkas, A.,Wolf, M.,Landzberg, E.,Woods, K.,Lynch, M.. Treatment of ventricular fibrillation due to ammonium bifluoride poisoning with hemodialysis. *Clinical Toxicology.* 2018. 56 (10):1063	One or more exclusion criteria
L1	Wang, X. Y.,Tao, F.,Xiao, D.,Lee, H.,Deen, J.,Gong, J.,Zhao, Y.,Zhou, W.,Li, W.,Shen, B.,Song, Y.,Ma, J.,Li, Z. M.,Wang, Z.,Su, P. Y.,Chang, N.,Xu, J. H.,Ouyang, P. Y.,von Seidlein, L.,Xu, Z. Y.,Clemens, J. D.. Trend and disease	One or more exclusion criteria

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L1	Sezgin, B. I.,Onur Ş, G.,Menteş, A.,Okutan, A. E.,Haznedaroğlu, E.,Vieira, A. R.. Two-fold excess of fluoride in the drinking water has no obvious health effects other than dental fluorosis. *J Trace Elem Med Biol.* 2018. 50:216-222	One or more exclusion criteria
L1	Gooch, B. F.. U.S. public health service recommendation for fluoride concentration in drinking water for the prevention of dental caries. *Public Health Reports.* 2015. 130:318-331	One or more exclusion criteria
L1	Singh, P.,Das, T. K.. Ultrastructural localization of 4-hydroxynonenal adducts in fluoride-exposed cells: Protective role of dietary antioxidants. *Fluoride.* 2019. 52:49-58	One or more exclusion criteria

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L1	Daly, N.,Farren, M.,McKeating, A.,Moffitt, K.,Sheehan, S. R.,Turner, M. J.. Universal screening for gestational diabetes mellitus (GDM) with a fasting plasma glucose measurement under strict preanalytical conditions at the first prenatal visit. *American Journal of Obstetrics and Gynecology.* 2016. 1):S169-S170	One or more exclusion criteria
L1	Wanigasuriya, K.. Update on uncertain etiology of chronic kidney disease in Sri Lanka's north-central dry zone. *MEDICC Rev.* 2014. 16:61-5	One or more exclusion criteria
L1	Degrossi, O. J.,Gutierrez, S.,Fadel, A.,Degrossi, E. B.,Valdivieso, M. C.,Balbuena, R. L.,Del, C. A. M.,De Cabrejas, M.. Uptake of 131-I in maxillary bones mimicking salivary glands. False- positive images in patients with Differentiated Thyroid Carcinoma. DTC. [Spanish]. *Revista Argentina de Endocrinologia y Metabolismo.* 2008. 45:67-74	One or more exclusion criteria
L1	Babiuch, K.,Pretzel, D.,Tolstik, T.,Vollrath, A.,Stanca, S.,Foertsch, F.,Becer, C. R.,Gottschaldt, M.,Biskup, C.,Schubert, U. S.. Uptake of well-defined, highly glycosylated, pentafluorostyrene-based polymers and nanoparticles by human hepatocellular carcinoma cells. *Macromol Biosci.* 2012. 12:1190-9	One or more exclusion criteria
L1	Diwan, V.,Sar, S. K.,Biswas, S.,Dewangan, R.,Baghel, T.. Uranium in ground water of Rajnandgaon District of Central India. *Journal of Radioanalytical and Nuclear Chemistry.* 2019. 321:293-302	One or more exclusion criteria

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L1	Srikanth, R.,Gautam, A.,Jaiswal, S. C.,Singh, P.. Urinary fluoride as a monitoring tool for assessing successful intervention in the provision of safe drinking water supply in five fluoride-affected villages in Dhar district, Madhya Pradesh, India. *Environmental Monitoring and Assessment.* 2013. 185:2343-2350	One or more exclusion criteria
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L1	Cox, K. D.,English, J. C.,Bhat, V.. Use of "read-across" and threshold of toxicological concern approaches to establish allowable concentrations in drinking water: A case study. *Toxicology Letters.* 2017. 280 (Supplement 1):S101	One or more exclusion criteria
L1	Renfrew, A. K.,Scopelliti, R.,Dyson, P. J.. Use of perfluorinated phosphines to provide thermomorphic anticancer complexes for heat-based tumor targeting. *Inorg Chem.* 2010. 49:2239-46	One or more exclusion criteria
L1	Samdan, N.. Use of some medicinal plants in ageing. *Wiener Klinische Wochenschrift.* 2009. 121:S80-S82	One or more exclusion criteria
L1	Campbell-Verduyn, L. S.,Mirfeizi, L.,Dierckx, R. A.,Elsinga, P. H.,Feringa, B. L.. Using "Click" Chemistry as a Tool for Fluorine-18 Radiolabelling of Bombesin. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2011. 1):S487	One or more exclusion criteria

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L1	Mirfeizi, L.,Campbell-Verduyn, L. S.,Yu, Z.,Feringa, B. L.,Dierckx, R. R.,De Jong, J. I.,Helfrich, W.,Elsinga, P. H.. Using copper free click chemistry for PET as a tool for fluorine-18 radiolabelling of Bombesin. *European Journal of Nuclear Medicine and Molecular Imaging.* 2011. 2):S208	One or more exclusion criteria
L1	Wang, Y.,Chen, X. D.,Wang, C. S.. Using inverse distance weighting in studying the distribution of endemic fluorosis in Jiangsu Province. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:97-100	One or more exclusion criteria
L1	Dubey, S. P.,Gopal, K.,Bersillon, J. L.. Utility of adsorbents in the purification of drinking water: A review of characterization, efficiency and safety evaluation of various adsorbents. *Journal of Environmental Biology.* 2009. 30:327-332	One or more exclusion criteria
L1	Risheq, F. Y.,Alrisheq, M. F.,Al-Sadoon, S. J.,Qwarik, A. A.. Utility of Delayed 18 FDG PET/CT imaging for lesions detection enhancement. *European Journal of Nuclear Medicine and Molecular Imaging.* 2015. 1):S395-S396	One or more exclusion criteria
L1	Bondu, J. D.,Selvakumar, R.,Fleming, J. J.. Validating a High Performance Liquid Chromatography-Ion Chromatography (HPLC-IC) Method with Conductivity Detection After Chemical Suppression for Water Fluoride Estimation. *Indian Journal of Clinical Biochemistry.* 2018. 33:86-90	One or more exclusion criteria

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L1	Chang, E. T.,Adami, H. O.,Bailey, W. H.,Boffetta, P.,Krieger, R. I.,Moolgavkar, S. H.,Mandel, J. S.. Validity of geographically modeled environmental exposure estimates. *Critical Reviews in Toxicology.* 2014. 44:450-466	One or more exclusion criteria
L1	Leslie, D. L.,Lyons, W. B.. Variations in Dissolved Nitrate, Chloride, and Sulfate in Precipitation, Reservoir, and Tap Waters, Columbus, Ohio. *Int J Environ Res Public Health.* 2018. 15:#pages#	One or more exclusion criteria
L1	Hari Kumar, K. V. S.,Singh, Y.. Visual vignette. *Endocrine Practice.* 2019. 25:1082	One or more exclusion criteria
L1	Tian, Y.,Xiao, Y.,Wang, B.,Sun, C.,Tang, K.,Sun, F.. Vitamin E and lycopene reduce coal burning fluorosis-induced spermatogenic cell apoptosis via oxidative stress-mediated JNK and ERK signaling pathways. *Bioscience Reports.* 2018. 38 (4) (no pagination):#pages#	One or more exclusion criteria
L1	Minana, I. V.. Vitamins and trace elements. *Pediatria Integral.* 2015. 19:324-336	One or more exclusion criteria

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L1	Su, L.,Zhang, Z.,Xiong, Y.. Water dispersed two-dimensional ultrathin Fe(iii)-modified covalent triazine framework nanosheets: peroxidase like activity and colorimetric biosensing applications. *Nanoscale.* 2018. 10:20120-20125	One or more exclusion criteria
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L1	Yeung, C. A.. Water fluoridation could save NHS millions every year. *BMJ (Online).* 2014. 348 (no pagination):#pages#	One or more exclusion criteria
L1	Rabb-Waytowich, D.. Water fluoridation in Canada: past and present. *J Can Dent Assoc.* 2009. 75:451-4	One or more exclusion criteria
L1	Osmunson, B.. Water fluoridation intervention: Dentistry's crown jewel or dark hour?. *Fluoride.* 2007. 40:214-221	One or more exclusion criteria
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L1	Connett, P.. Water fluoridation--a public health hazard. *Int J Occup Environ Health.* 2006. 12:88-91	One or more exclusion criteria

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L1	Peckham, S.,Awofeso, N.. Water fluoridation: A critical review of the physiological effects of ingested fluoride as a public health intervention. *The Scientific World Journal.* 2014. 2014 (no pagination):#pages#	One or more exclusion criteria
L1	Amenu, K.,Markemann, A.,Valle Zárate, A.. Water for human and livestock consumption in rural settings of Ethiopia: assessments of quality and health aspects. *Environ Monit Assess.* 2013. 185:9571-86	One or more exclusion criteria
L1	Fang, J.,Wu, X.,Xu, J.,Yang, X.,Song, X.,Wang, G.,Yan, M.,Yan, M.,Wang, D.. Water management challenges in the context of agricultural intensification and endemic fluorosis: the case of Yuanmou County. *Ecohealth.* 2011. 8:444-55	One or more exclusion criteria
L1	Pinto, U.,Thoradeniya, B.,Maheshwari, B.. Water quality and chronic kidney disease of unknown aetiology (CKDu) in the dry zone region of Sri Lanka: impacts on well-being of village communities and the way forward. *Environmental science and pollution research international.* 2020. 27:3892-3907	One or more exclusion criteria
L1	Bermejo, I. A.,Usabiaga, I.,Compañón, I.,Castro-López, J.,Insausti, A.,Fernández, J. A.,Avenoza, A.,Busto, J. H.,Jiménez-Barbero, J.,Asensio, J. L.,Peregrina, J. M.,Jiménez-Osés, G.,Hurtado-Guerrero, R.,Cocinero, E. J.,Corzana, F.. Water Sculpts the Distinctive Shapes and Dynamics of the Tumor-Associated Carbohydrate Tn Antigens: Implications for Their Molecular Recognition. *J Am Chem Soc.* 2018. 140:9952-9960	One or more exclusion criteria

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L1	Varol, E.,Varol, S.. Water-borne fluoride and primary hypertension. *Fluoride.* 2013. 46:3-6	One or more exclusion criteria
L1	Nemoto, A.,Chosa, N.,Kyakumoto, S.,Yokota, S.,Kamo, M.,Noda, M.,Ishisaki, A.. Water-soluble factors eluated from surface pre-reacted glass-ionomer filler promote osteoblastic differentiation of human mesenchymal stem cells. *Mol Med Rep.* 2018. 17:3448-3454	One or more exclusion criteria
L1	Ogbu, I. S. I.,Okoro, O. I. O.,Ugwuja, E. I.. Well waters fluoride in Enugu, Nigeria. *International Journal of Occupational and Environmental Medicine.* 2012. 3:96-98	One or more exclusion criteria
L1	Samstein, M.,Kaplan, B.,Ponda, P.. What's Not in the Water? Pseudoallergic Reactions to Niacinamide Containing Flouridated Multivitamins. *Annals of Allergy, Asthma and Immunology.* 2019. 123 (5 Supplement):S67	One or more exclusion criteria
L1	Armfield, J. M.. When public action undermines public health: A critical examination of antifluoridationist literature. *Australia and New Zealand Health Policy.* 2007. 4 (1) (no pagination):#pages#	One or more exclusion criteria
L1	Baysoy, G.,Uzulmez, R. H.. Who is your dietitian? Diet of breastfeeding mothers with an allergic infant lacks many essential nutrients. *Journal of Pediatric Gastroenterology and Nutrition.* 2018. 66 (Supplement 2):981	One or more exclusion criteria

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L1	Wasana, H. M.,Perera, G. D.,Gunawardena, P. S.,Fernando, P. S.,Bandara, J.. WHO water quality standards Vs Synergic effect(s) of fluoride, heavy metals and hardness in drinking water on kidney tissues. *Sci Rep.* 2017. 7:42516	One or more exclusion criteria
L1	Johansson, E.,Lubberink, M.,Heurling, K.,Eriksson, J. W.,Skrtic, S.,Ahlstrom, H.,Kullberg, J.. Whole-body imaging of tissue-specific insulin sensitivity and body composition by using an integrated PET/MR system: A feasibility study. *Radiology.* 2018. 286:271-278	One or more exclusion criteria
L1	Kennett, J.. Will routine use of statins after age 50 become as common as fluoridating drinking water? It should!. *Mo Med.* 2013. 110:342-3	One or more exclusion criteria
L1	Huang, C. Q.. X-ray signs of bone and joint among residents of endemic fluorosis area 40 years after improvement of water. [Chinese]. *Chinese Journal of Endemiology.* 2006. 25:192-195	One or more exclusion criteria
L1	Huang, C. Q.. X-rays changes of forearm and shank of residents from areas with different fluoride contents in drinking water in Jilin province. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:208-212	One or more exclusion criteria
L1	Li, Z.,Jia, K.,Duan, Y.,Wang, D.,Zhou, Z.,Dong, S.. Xanomeline derivative EUK1001 attenuates Alzheimer's disease pathology in a triple transgenic mouse model. *Mol Med Rep.* 2017. 16:7835-7840	One or more exclusion criteria
L1	Venault, A.,Lin, K. H.,Tang, S. H.,Dizon, G. V.,Hsu, C. H.,Maggay, I. V. B.,Chang, Y.. Zwitterionic electrospun PVDF fibrous membranes with a well-	One or more exclusion criteria

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	controlled hydration for diabetic wound recovery. *Journal of Membrane Science.* 2020. 598 (no pagination):#pages#	
L2	Bian, J.,Lin, X.,Yang, X.,Fan, T.,Zhu, Q.. [Changes of certain oxidative, anti-oxidative and vascular function indexes of New Zealand rabbit exposed by high-fluoride]. [Chinese]. *Wei sheng yan jiu = Journal of hygiene research.* 2010. 39:751-754	Non-English publication
L2	Biloklyts'ka, H. F.,Pohrebniak, H. V.,Khalili, D.. [Effect of the diet with different microelement composition on the state of alveolar and pelvic bones in rats]. *Fiziol Zh.* 2008. 54:74-8	Non-English publication
L2	Chen, C.,Lu, Y.,Wang, S. Y.,Li, X. H.. Research on residual alveolar bone in fluorosis rats. [Chinese]. *Journal of Xi'an Jiaotong University (Medical Sciences).* 2012. 33:110-113	Non-English publication
L2	Chen, R.,Zhu Li De Zi, T.,Zhao, L.,Tian, J. G.,Ruan, J. P.. Effects of fluoride on the expressions of MMP-20 and KLK4 in rat ameloblasts. [Chinese]. *Journal of Xi'an Jiaotong University (Medical Sciences).* 2013. 34:433-436	Non-English publication
L2	Chen, X. S.,Yu, Y. N.,Yi, W.,Wan, L. B.,Xie, Y.. Effect of fluoride on expression of mRNA and protein of Wnt3a and beta-catenin in osteoblast of rats. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:140-145	Non-English publication

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L2	Chen, X. Y.,Liang, B.,Tang, F. W.,Zhang, Y. C.,Sun, F.,Gu, J.,Zhang, S.. Role of stanniocalcin 1 in brain injury of coal-burning-borne fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:129-132	Non-English publication
L2	Cui, Y. S.,Zhong, Q.,Li, W. F.,Liu, Z. H.,Wang, Y.,Hou, C. C.. [Effects of fluoride exposure on thyroid hormone level and intelligence in rats]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi.* 2017. 35:888-892	Non-English publication
L2	Deng, C. N.,Yu, Y. N.,Xie, Y.,Zhao, L. N.. [Expression of calcineurin and nuclear factor of activated T cells 1 in testis of rats with chronic fluorosis]. [Chinese]. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine].* 2013. 47:1142-1147	Non-English publication
L2	Deng, C. N.,Yu, Y. N.,Yang, D.,Zhu, H. Z.. Expression of nuclear factor kappa B-related mRNA and protein in bone tissue of fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:135-139	Non-English publication
L2	Deng, C. N.,Yu, Y. N.,Yang, D.,Zhu, H. Z.. Relationship of nuclear factor kappa B-related gene expression and osteoclast apoptosis induced by fluoride in bone tissue. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:518-522	Non-English publication
L2	Deng, C. N.,Zhang, Y.,Xu, L.,Zhao, L. N.,Linghu, Y.,Yu, Y. N.. [Change and relationship between Gli1 and beta-catenin on rats' bone formation with chronic fluorosis]. *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology.* 2020. 49:168-173	Non-English publication

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L2	Deng, C.,Yu, Y.,Zhang, Y.. Expressions of transforming growth factor-beta1 and interleukin 6 mRNA and protein in bone of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:609-614	Non-English publication
L2	Dong, Y.,Wang, Y.,Wei, N.,Guan, Z.. Expression levels of brain muscarinic acetylcholine receptor in offspring rats of drinking-water borne fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2015. 34:326-330	Non-English publication
L2	Dong, Y.,Wang, Y.,Wei, N.,Guan, Z.. Expression of muscarinic acetylcholine receptors in the brain of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2015. 34:84-88	Non-English publication
L2	Ersan, Y.,Koc, E.,Ari, I.,Karademir, B.. Histopathological effects of chronic fluorosis on the liver of mice (Swiss albino). [Turkish]. *Turkish Journal of Medical Sciences.* 2010. 40:619-622	Non-English publication
L2	Fan, S. L.,Bai, S. B.,Qin, W.,Zhang, Y. L.,Zhong, J. J.,Chen, R.,Li, T.,Feng, S. M.,Liu, K. T.,Luo, X. G.,Chen, L.,Liao, L. B.. Morphological changes of bone in the progress of rat chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:151-155	Non-English publication
L2	Gao, Q.,Liu, Y. J.,Wu, C. X.,Long, Y. G.,Guan, Z. Z.. Level of oxidative stress in rat brains and learning and memory function of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:371-373	Non-English publication

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L2	Gao, Y. H.,Sun, D. J.,Zhou, L. W.,Yu, J.,Li, Y.,Wang, Y.. Effect of subchronic fluoride intoxication on inducible nitric oxide synthase expression in rat bone tissue. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:124-127	Non-English publication
L2	Gui, C. Z.,Ran, L. Y.,Guan, Z. Z.. Expression levels of brain nicotinic acetylcholine receptor mRNA and protein in coal-burning type of fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:239-242	Non-English publication
L2	Guo, X.,Wu, S.,He, Y.,Zhang, Z.,Sun, G.. [Effect of subchronic fluoride exposure on pathologic change and beta-catenin expression in rat bone tissue]. [Chinese]. *Wei sheng yan jiu = Journal of hygiene research.* 2011. 40:304-307	Non-English publication

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L2	Kelimu, A.,Liu, K. T.,Lian, J.,Hu, H. H.,Zheng, Y. J.,Wang, T. M.. Effects of vitamin C and E on the ultrastructure in liver, kidney and brain of fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:378-381	Non-English publication
L2	Li, H.,Cai, Q.,Wang, D.. Effects of fluoride on rat thyroid morphology, thyroid peroxidase activity and the expression of thyroid peroxidase protein. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:271-274	Non-English publication
L2	Li, J. Y.,Liang, Z. P.,Ma, H. S.. Changes of the femur biomechanics in fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:154-156	Non-English publication

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L2	Liu, Y. J.,Gao, Q.,Wu, C. X.,Long, Y. G.,Guan, Z. Z.. Modified expression of extracellular signal-regulated protein kinase signal transduction in rat brains and changed capacity of learning and memory of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:32-35	Non-English publication
L2	Lou, D. D.,Liu, Y. F.,Qin, S. L.,Zhang, K. L.,Yu, Y. N.,Guan, Z. Z.. Changed transcription level of mitochondrial fission and fusion gene loci in cortical neurons of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:125-129	Non-English publication
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L2	Lou, D. D.,Pan, J. G.,Zhang, K. L.,Qin, S. L.,Liu, Y. F.,Yu, Y. N.,Guan, Z. Z.. [Changed expression of mito-fusion 1 and mitochondrial fragmentation in the	Non-English publication

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L2	Lou, D. D.,Zhang, K. L.,Qin, S. L.,Liu, Y. F.,Liu, Y. J.,Guan, Z. Z.. Effects of chronic fluorosis on 4.8 kb mitochondrial DNA in liver, kidney and brain of rats. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:121-124	Non-English publication
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L2	Mei, M.,Yu, Y. N.,Guo, B.. Effect of fluoride on expression of Runx2 mRNA and protein in bone tissue of rats. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:493-495	Non-English publication
L2	Mo, F.,Qu, W.,Xia, S. H.,Yu, M. J.,Tu, F.. Effects of soybean, selenium and spirulina on hemoglobin of rats intoxicated with fluorine and aluminium. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:384-386	Non-English publication
L2	Ortega Garcia, J. A.,Ferris, I. Tortajada J.,Berbel Tornero, O.,Romero, K. J.,Rubalcava, L.,Martinez Salcedo, E.,Apolinar Valiente, E.,Crehua Gaudiza,	Non-English publication

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L2	Qin, S.,Lou, D. D.,Liu, Y. F.,Yu, Y. N.,Guan, Z. Z.. Expression of mitochondrial fission protein locus Fis1 and ultrastructural changes in the renal cells of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:125-128	Non-English publication
L2	Qiu, Y. H.,Kong, D. M.,Yang, Q.,Zhao, N.. Influence of high-fluoride on thyroid function and brain damage in rats. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:146-149	Non-English publication
L2	Shen, Q. F.,Li, H. N.,Xu, T. T.,Xia, Y. P.. Damage of blood brain barrier of spinal cord in rats with chronic fluorosis. [Chinese]. *National Medical Journal of China.* 2012. 92:2357-2361	Non-English publication

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L2	Sun, J. C.,Wang, C. Y.,Xu, H.,Li, G. S.. Effect of endoplasmic reticulum stress in renal injury of fluorosis rats. [Chinese]. *Journal of Jilin University Medicine Edition.* 2009. 35:992-995	Non-English publication
L2	Tang, L.,Bai, S. B.,Zhang, Y. L.,Liu, K. T.,Zhang, Y. X.,Jin-jie, Z.. Experimental study of cartilage lesions and COLIXA 3 protein expression in rats cartilage with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:389-392	Non-English publication
L2	Tao, H.,Wang, L.,Hou, T. Z.,Zhang, L.,Wang, X. R.. Ameloblastin gene expression in fluoride-induced mus musculus incisors in mice. [Chinese]. *Journal of Xi'an Jiaotong University (Medical Sciences).* 2011. 32:238-241	Non-English publication
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L2	Wei, N.,Dong, Y.,Wang, Y.,Guan, Z.. Effects of chronic fluorosis on neurobehavioral development in offspring of rats and antagonistic effect of Vitamin E. [Chinese]. *Chinese Journal of Endemiology.* 2014. 33:125-128	Non-English publication
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L2	Xiao, Y. M.,Sun, X. J.,Yu, Y. N.. Effect of fluoride on the expression of osteoprotegerin/receptor activator of nuclear factor kappabeta ligand/receptor activator of nuclear factor kappabeta system proteins of rats with fluorosis and the antagonism of Danlan Xianpeng capsule. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:487-492	Non-English publication
L2	Xie, Y.,Yu, Y. N.,Wan, L. B.,Chen, X. S.. Effect of fluoride on expression of CaN mRNA and protein in bone tissue of rats. [Chinese]. *Chinese Journal of Pathology.* 2012. 41:761-764	Non-English publication
L2	Xu, H.,Fan, H. Q.,Zhang, J. M.,Li, G. S.. Study on oxidative stress and activity of alkaline phosphatase of rats exposed to different period of fluoride. [Chinese]. *Chinese Journal of Endemiology.* 2010. 29:124-126	Non-English publication

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L2	Xu, H.,Zhao, Z. T.,Jing, L.,Li, G. S.. Study on endoplasmic reticulum stress in bone tissue of fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2009. 28:36-40	Non-English publication
L2	Xu, P.,Yao, J.,Cai, Q.,Zhang, Y.,Du, X.,Guo, X.. Preventive effect of the supplemental dietary boron on bone damage of rats with excess fluoride ingestion. [Chinese]. *Journal of Xi'an Jiaotong University (Medical Sciences).* 2008. 29:625-628	Non-English publication
L2	Yang, L. P.,Wang, K. Y.,Shi, X. Q.,Li, H.. Joint effects of fluoride and aluminum on biomarkers of bone metabolism in mice. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:374-377	Non-English publication
L2	Yang, L. P.,Wang, K. Y.,Shi, X. Q.,Li, H.. Study on pathology and histomorphometry of mouse bone in combined intoxication of fluoride and aluminum. [Chinese]. *Chinese Journal of Endemiology.* 2008. 27:137-140	Non-English publication
L2	Yang, M.,Ren, Z.,Zhou, B.,Guan, Z.,Yu, W.. Expression of endonuclease G in the brain tissue of rats with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2017. 36:327-332	Non-English publication

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L2	Yi, G. K.,Liu, L.,Li, X. Z.. Over-dose fluoride induces the degeneration and ossification of the ligamentum flavum. [Chinese]. *Chinese Journal of Tissue Engineering Research.* 2015. 19:5301-5305	Non-English publication
L2	Yuan, X. J.,Liu, N. Y.,Ma, F. H.,Suo, F.,Chen, J. M.,Yang, F.. Effect of selenium-germenium agent on antioxidase and major elements in fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2007. 26:137-139	Non-English publication
L2	Zhang, K. L.,Lou, D. D.,Guan, Z. Z.. Changes of syndecan-4 and nuclear factor kappaB in the kidney of rat with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:133-135	Non-English publication
L2	Zhang, K. L.,Lou, D. D.,Guan, Z. Z.. Expression of receptor for advanced glycation endproducts and nuclear factor kappaB in brain hippocampus of rat with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2013. 32:625-628	Non-English publication
L2	Zhang, K. L.,Lou, D. D.,Liu, Y. F.,Qin, S. L.,Guan, Z. Z.. Changes of P-glycoprotein and nuclear factor kappaB in the cerebral cortex of rat with chronic fluorosis. [Chinese]. *Chinese Journal of Endemiology.* 2012. 31:613-616	Non-English publication

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L2	Zhang, W. L.,Xue, L. J.,Cui, Y. N.,Li, G. S.. The effect of different dosage of fluoride intake on activation of osteoblasts and the expression of BMP-2, BMP-4 and Smad-4. [Chinese]. *Chinese Journal of Endemiology.* 2006. 25:125-128	Non-English publication
L2	Zhang, X. Y.,Lu, P.,Zhang, J. M.,Zhao, Z. T.,Xu, H.,Li, G. S.. Immunoglobulin binding protein gene and protein expression in femur tissue of fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:502-505	Non-English publication
L2	Zhao, Q.,Wu, Y.,Zhang, Z. G.,Yang, S. P.. Protective effect of selenium on fluoride-induced renal impairments in rats. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:137-141	Non-English publication
L2	Zhu, H. Z.,Yu, Y. N.,Deng, C. N.,Yang, D.. Effect of fluoride on expression of phosphoinositide 3-kinase, protein kinase B1 mRNA and protein in bone tissue of rats. [Chinese]. *Chinese Journal of Endemiology.* 2011. 30:261-265	Non-English publication
L2	Zhu, Z.,Yu, Y.,Too, X.,Zhao, L.. Expression of Janus kinase/signal transduction and transcriptional activation (JAK1 and STAT3) in liver of fluorosis rats. [Chinese]. *Chinese Journal of Endemiology.* 2015. 34:733-738	Non-English publication
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L2	Anonymous,. Translations of twelve Chinese studies on developmental fluoride neurotoxicity. *Fluoride.* 2008. 41:111-114	Full-text not available
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L2	Brun, L. R.,Roma, S. M.,Perez, F.,Rigalli, A.. Inflammation in rat bone induced by sodium fluoride. *Actualizaciones en Osteologia.* 2012. 8:19-28	Full-text not available
L2	Choi, A. L.,Sun, G.,Zhang, Y.,Grandjean, P.. Meta-analysis of 27 studies of fluoride neurotoxicity in children. *Epidemiology.* 2012. 1):S25	Full-text not available
L2	de Carvalho, J. G.,Cestari, T. M.,de Oliveira, R. C.,Buzalaf, M. A. R.. Fluoride effects on ectopic bone formation in young and old rats. *Methods and Findings in Experimental and Clinical Pharmacology.* 2008. 30:287-294	Full-text not available
L2	de Carvalho, J. G.,Cestari, T. M.,de Oliveira, R. C.,Buzalaf, M. A.. Fluoride effects on ectopic bone formation in young and old rats. *Methods Find Exp Clin Pharmacol.* 2008. 30:287-94	Full-text not available
L2	Fina, B. L.,Lupo, M.,DaRos, E. R.,Moreno, H.,Roma, S. M.,Rigalli, A.. Effect of sodium fluoride on biomechanical and histomorphometric bone parameters: Identification of variables that determine the fracture load in NaF-treated rats. *Fluoride.* 2012. 45 (3 PART 1):163-164	Full-text not available

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L2	Guan, Z. Z.,Liu, Y. J.,Gui, C. Z.,Ran, L. Y.,Gao, Q.. Changed cholinergic system and neuronal signal transduction in rats with deficit of learning and memory induced by chronic fluorosis. *Fluoride.* 2012. 45 (3 PART 1):166-167	Full-text not available
L2	Han, H.,Sun, Z.,Luo, G.,Wang, C.,Wei, R.,Wang, J.. Fluoride exposure changed the structure and the expressions of reproductive related genes in the hypothalamus-pituitary-testicular axis of male mice. *Chemosphere.* 2015. 135:297-303	Full-text not available
L2	Jetti, R.,Raghuveer, C. V.,Chamallamudi, M. R.,Somayaji, S. N.,Billakanti, P. B.. Ameliorative effect of ginkgo biloba on neurodegeneration caused by fluoride. *Annals of Anatomy.* 2014. 1):62	Full-text not available
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L2	Krook, L. P.,Justus, C.. Erratum: Fluoride poisoning of horses from artificially fluoridated drinking water (Flouride (2006) 39, 1 (1-3)). *Fluoride.* 2006. 39:156	Full-text not available
L2	Losso, E. M.,Pereira, M.,Dombrowski, P. A.,Da Cunha, C.,Andreatini, R.. Sodium fluoride induced memory impairment is associated with changes in striatal monoamlnerglc levels. *European Neuropsychopharmacology.* 2009. 3):S329-S330	Full-text not available

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L2	Luis, H.. Commentary. *Journal of Neurosciences in Rural Practice.* 2012. 3:151	Full-text not available
L2	Manna, P.,Sinha, M.,Sil, P. C.. A 43 kD protein isolated from the herb Cajanus indicus L attenuates sodium fluoride-induced hepatic and renal disorders in vivo. *J Biochem Mol Biol.* 2007. 40:382-95	Full-text not available
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L2	Raju, S.,Sivanesan, S.,Gudemalla, K.,Mundugaru, R.,Swaminathan, M.. Effect of ginkgo biloba extract on hematological and biochemical alterations in fluoride intoxicated wistar rats. *Research Journal of Pharmacy and Technology.* 2019. 12:3839-3846	Full-text not available
L2	Ranjan, R.,Swarup, D.,Patra, R. C.,Varshney, V. P.. Changes in cortisol, oxidative stress indices, and serum biochemistry in fluoride-intoxicated rabbits. *Fluoride.* 2012. 45 (3 PART 1):191	Full-text not available
L2	Shankar, P.,Khandare, A. L.. Regulation and reversal of effects of fluoride on calcium homeostasis in rats. *Fluoride.* 2012. 45 (3 PART 1):198-199	Full-text not available

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L2	Shanthakumari, D.,Srinivasalu, S.,Subramanian, S.. Effect of fluoride intoxication on the levels of intestinal antioxidants studied in rats. *Methods & Findings in Experimental & Clinical Pharmacology.* 2007. 29:93-9	Full-text not available
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L2	Singh, P. K.,Feroz, A. D.,Sheeba, H.,Khalil, A.,Samir, A. M.. Beneficial effect of Tamarindus indica on the testes of albino rat after fluoride intoxication. *International Journal of Pharma and Bio Sciences.* 2012. 3:B487-B493	Full-text not available
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L2	Spittle, B. J.. Fluoride-induced cell ultrastructure changes. *Fluoride.* 2012. 45 (3 PART 1):201-203	Full-text not available
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L2	Cardenas-Gonzalez, M.,Jacobo Estrada, T.,Rodriguez-Munoz, R.,Barrera-Chimal, J.,Bobadilla, N. A.,Barbier, O. C.,Del Razo, L. M.. Sub-chronic exposure to fluoride impacts the response to a subsequent nephrotoxic treatment with gentamicin. *Journal of Applied Toxicology.* 2016. 36:309-19	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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L2	Chai, L.,Dong, S.,Zhao, H.,Deng, H.,Wang, H.. Effects of fluoride on development and growth of Rana chensinensis embryos and larvae. *Ecotoxicology and Environmental Safety.* 2016. 126:129-137	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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L2	Jianjie, C.,Wenjuan, X.,Jinling, C.,Jie, S.,Ruhui, J.,Meiyan, L.. Fluoride caused thyroid endocrine disruption in male zebrafish (Danio rerio). *Aquatic Toxicology.* 2016. 171:48-58	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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L2	Lu, J.,Xu, Q.,Zheng, J.,Liu, H.,Li, J.,Chen, K.. Comparative proteomics analysis of cardiac muscle samples from pufferfish Takifugu rubripes exposed to excessive fluoride: Initial molecular response to fluorosis Cardiac muscle proteomics of fish Jian Lu et al. *Toxicology Mechanisms and Methods.* 2009. 19:468-475	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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L2	Mukhopadhyay, D.,Priya, P.,Chattopadhyay, A.. Sodium fluoride affects zebrafish behaviour and alters mRNA expressions of biomarker genes in the brain: Role of Nrf2/Keap1. *Environmental Toxicology and Pharmacology.* 2016. 40:352-359	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Nabavi, S. F.,Eslami, S.,Moghaddam, A. H.,Nabavi, S. M.. Protective effects of curcumin against fluoride-induced oxidative stress in the rat brain. *Neurophysiology.* 2011. 43:287-291	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Nabavi, S. F.,Moghaddam, A. H.,Eslami, S.,Nabavi, S. M.. Protective effects of curcumin against sodium fluoride-induced toxicity in rat kidneys. *Biological Trace Element Research.* 2012. 145:369-374	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)

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L2	Nabavi, S. F.,Moghaddam, A. H.,Nabavi, S. M.,Eslami, S.. Protective effect of curcumin and quercetin on thyroid function in sodium fluoride intoxicated rats. *Fluoride.* 2011. 44:147-152	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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L2	Palczewska-Komsa, M.,Kalisinska, E.,Kosik-Bogacka, D. I.,Lanocha, N.,Budis, H.,Baranowska-Bosiacka, I.,Gutowska, I.,Chlubek, D.. Fluoride accumulation in dog bones. *Fluoride.* 2014. 47:98-108	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)

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L2	Ranjan, R.,Swarup, D.,Patra, R. C.. Changes in levels of zinc, copper, cobalt, and manganese in soft tissues of fluoride-exposed rabbits. *Fluoride.* 2011. 44:83-88	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Santoyo-Sanchez, M. P.,Del Carmen Silva-Lucero, M.,Arreola-Mendoza, L.,Barbier, O. C.. Effects of acute sodium fluoride exposure on kidney function, water homeostasis, and renal handling of calcium and inorganic phosphate. *Biological Trace Element Research.* 2013. 152:367-372	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Sarkar, S. D.,Maiti, R.,Ghosh, D.. Management of fluoride induced testicular disorders by calcium and vitamin-E co-administration in the albino rat. *Reprod Toxicol.* 2006. 22:606-12	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Schieferstein, H.,Betzel, T.,Haller, S.,Cindy, F.,Muller, C.,Ross, T. L.. Total evaluation of a new polar 18F-labeled PEG-click-folate. *Journal of Labelled Compounds and Radiopharmaceuticals.* 2013. 1):S183	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Shashi, A.,Bhushan, B.,Bhardwaj, M.. Histochemical pattern of gastrocnemius muscle in fluoride toxicity syndrome. *Asian Pacific Journal of Tropical Medicine.* 2010. 3:136-140	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)

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L2	Shi, X.,Zhuang, P.,Zhang, L.,Feng, G.,Chen, L.,Liu, J.,Qu, L.,Wang, R.. The bioaccumulation of fluoride ion (F(-)) in Siberian sturgeon (Acipenser baerii) under laboratory conditions. *Chemosphere.* 2009. 75:376-80	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Singh, R.,Hussain, M. A.,Kumar, J.,Kumar, M.,Kumari, U.,Mazumder, S.. Chronic fluoride exposure exacerbates headkidney pathology and causes immune commotion in Clarias gariepinus. *Aquat Toxicol.* 2017. 192:30-39	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Singh, R.,Khatri, P.,Srivastava, N.,Jain, S.,Brahmachari, V.,Mukhopadhyay, A.,Mazumder, S.. Fluoride exposure abates pro-inflammatory response and induces in vivo apoptosis rendering zebrafish (Danio rerio) susceptible to bacterial infections. *Fish Shellfish Immunol.* 2017. 63:314-321	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Srilatha, K.,Banji, D.,Banji, O. J. F.,Vinod, K. R.,Saidulu, A.. Investigation on the anti-genotoxic effect of Ocimum Sanctum in Fluoride induced genotoxicity. *International Research Journal of Pharmacy.* 2013. 4:160-164	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)

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L2	Thammitiyagodage, M. G.,De Silva, N. R.,Rathnayake, C.,Karunakaran, R.,Wgss, K.,Gunatillka, M. M.,Ekanayaka, N.,Galhena, B. P.,Thabrew, M. I.. Biochemical and histopathological changes in Wistar rats after consumption of boiled and un-boiled water from high and low disease prevalent areas for chronic kidney disease of unknown etiology (CKDu) in north Central Province (NCP) and its comparison with low disease prevalent Colombo, Sri Lanka. *BMC Nephrology.* 2020. 21 (1) (no pagination):#pages#	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Thammitiyagodage, M. G.,Gunatillaka, M. M.,Ekanayaka, N.,Rathnayake, C.,Horadagoda, N. U.,Jayathissa, R.,Gunaratne, U. K.,Kumara, W. G.,Abeynayake, P.. Ingestion of dug well water from an area with high prevalence of chronic kidney disease of unknown etiology (CKDu) and development of kidney and liver lesions in rats. *Ceylon Med J.* 2017. 62:20-24	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Vasant, R. A.,Narasimhacharya, A. V. R. L.. Alleviation of fluoride-induced hepatic and renal oxidative stress in rats by the fruit of Limonia acidissima. *Fluoride.* 2011. 44:14-20	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Vasant, R. A.,Narasimhacharya, A. V. R. L.. Ameliorative effect of tamarind leaf on fluoride-induced metabolic alterations. *Environmental Health and Preventive Medicine.* 2012. 17:484-493	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)

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L2	Yu, Z.,Xu, C.,Yuan, K.,Gan, X.,Feng, C.,Wang, X.,Zhu, L.,Zhang, G.,Xu, D.. Characterization and adsorption mechanism of ZrO(2) mesoporous fibers for health-hazardous fluoride removal. *J Hazard Mater.* 2018. 346:82-92	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Broadbent, J. M.,Thomson, W. M.,Moffitt, T. E.,Poulton, R.. Health effects of water fluoridation: A response to the letter by Menkes et al. *New Zealand Medical Journal.* 2015. 128:73-74	Human subjects
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L2	Choi, A. L.,Sun, G.,Zhang, Y.,Grandjean, P.. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect.* 2012. 120:1362-8	Human subjects
L2	Yeung, C. A.. A systematic review of the efficacy and safety of fluoridation. *Evid Based Dent.* 2008. 9:39-43	Human subjects
L2	Yin, X. H.,Huang, G. L.,Lin, D. R.,Wan, C. C.,Wang, Y. D.,Song, J. K.,Xu, P.. Exposure to fluoride in drinking water and hip fracture risk: a meta-analysis of observational studies. *PLoS One.* 2015. 10:e0126488	Human subjects

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L2	Matsui, H.,Morimoto, M.,Horimoto, K.,Nishimura, Y.. Some characteristics of fluoride-induced cell death in rat thymocytes: cytotoxicity of sodium fluoride. *Toxicology in Vitro.* 2007. 21:1113-20	In-vitro models (mammalian cells/ tissues, bacterial cells, plant cells etc.)
L2	Oliveira, R. C. D.,Matsuda, S. S.,Silva, T. L. D.,Buzalaf, M. A. R.. Effects of sodium fluoride during osteoblasts mineralization in C57BL/6J and C3H/HeJ inbred strains of mice. *Bone.* 2012. 1):S84	In-vitro models (mammalian cells/ tissues, bacterial cells, plant cells etc.)
L2	Choubisaa, S. L.. A brief and critical review of endemic hydrofluorosis in Rajasthan, India. *Fluoride.* 2018. 51:13-33	Non-systematic review
L2	Dhar, V.,Bhatnagar, M.. Physiology and toxicity of fluoride. *Indian J Dent Res.* 2009. 20:350-5	Non-systematic review
L2	Dharmaratne, R. W.. Exploring the role of excess fluoride in chronic kidney disease: A review. *Human and Experimental Toxicology.* 2019. 38:269-279	Non-systematic review
L2	Gouri Pratusha, N.,Banji, O. J. F.,Banji, D.,Ragini, M.,Pavani, B.. Fluoride toxicity - A harsh reality. *International Research Journal of Pharmacy.* 2011. 2:79-85	Non-systematic review
L2	Kabir, H.,Gupta, A. K.,Tripathy, S.. Fluoride and human health: Systematic appraisal of sources, exposures, metabolism, and toxicity. *Critical Reviews in Environmental Science and Technology..* 2019. #volume#:#pages#	Non-systematic review

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L2	Prystupa, J.. Fluorine - A current literature review. An NRC and ATSDR based review of safety standards for exposure to fluorine and fluorides. *Toxicology Mechanisms and Methods.* 2011. 21:103-170	Non-systematic review
L2	Sharma, D.,Singh, A.,Verma, K.,Paliwal, S.,Sharma, S.,Dwivedi, J.. Fluoride: A review of pre-clinical and clinical studies. *Environ Toxicol Pharmacol.* 2017. 56:297-313	Non-systematic review
L2	Strunecka, A.,Strunecky, O.. Chronic Fluoride Exposure and the Risk of Autism Spectrum Disorder. *Int J Environ Res Public Health.* 2019. 16:#pages#	Non-systematic review
L2	Barbier, O.,Cardenas-Gonzalez, M.,Parada-Cruz, B.,Lopez, V. D.,Jimenez-Cordova, M.,Solis-Angeles, S.,Del Razo, L. M.. Fluoride: An underestimated nephrotoxic. *Toxicology Letters.* 2016. 259 (Supplement 1):S13	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Burgstahler, A. W.,Freeman, R. F.,Jacobs, P. N.. Toxic effects of silicofluoridated water in chinchillas, caimans, alligators, and rats held in captivity. *Fluoride.* 2008. 41:83-88	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Cardenas-Gonzalez, C.,Del Razo, L. M.,Barbier, O.,Jacobo, T.. Effect of nephrotoxic treatment with gentamicin on rats exposed to fluoride. *Toxicology Letters.* 2012. 1):S4	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation

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L2	Choi, A. L.,Grandjean, P.,Sun, G.,Zhang, Y.. Developmental fluoride neurotoxicity: Choi et al. Respond. *Environ Health Perspect.* 2013. 121:A70	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Dian, B. J.,Selvakumar, R.,Joseph, F. J.,Teresa, M. M.,Thomas, V. P.,Sheshadri, M. S.. Does Vitamin D Deficiency and Renal Dysfunction play a role in the pathogenesis of Fluorotoxic Metabolic Bone Disease (FMBD). *Indian Journal of Endocrinology and Metabolism.* 2017. 21 (7 Supplement 1):65	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Fina, B. L.,Rigalli, A.. Effect of fluoride on oxygen consumption (OC) by rat tissues. *Bone.* 2011. 48 (6):S284	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
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L2	Gama-Dominguez, Y.,Jacobo-Estrada, T.,Lopez-Ventura, D.,Moreno-Licona, N. J.,Trevino, S.,Barbier, O.. Effect of renal ischemia on sub-chronically exposed rats to fluoride evaluated by the expression of hypoxia-inducible factor 1alpha (HIF-1alpha). *Toxicology Letters.* 2016. 259 (Supplement 1):S241-S242	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Iano, F. G.,Ferreira, M. C. F.,Fernandes, M.,Oliveira, R.,Ximenes, V. F.,Buzalaf, M. A. R.. Chronic toxicity of fluoride in the Liver antioxidant defense. *Free Radical Biology and Medicine.* 2010. 1):S221	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation

Level	Bibliography	Reason for Exclusion
L2	Iano, F. G.,Ferreira, M. C. F.,Quaggio, G. B.,Oliveira, R. C.,Ximenes, V. F.,Buzalaf, M. A. R.. Effect of fluoride in antioxidant systems of the heart. *Free Radical Biology and Medicine.* 2011. 1):S57	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Jain, A.,Mehta, V. K.,Mahdi, A. A.,Bhatnagar, M.. The effects of fluoride and arsenic exposure on the cholinergic-nitrergic system, cognitive functions and inflammatory markers. *Journal of Neurochemistry.* 2015. 1):141-142	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Khalili, J.,Biloklytska, H.. The activity of fructose diphosphatase and acid-base status in rats exposed to fluoride and ammonium chloride. *Toxicology Letters.* 2009. 1):S108-S109	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Krook, L. P.,Justus, C.. Fluoride poisoning of horses from artificially fluoridated drinking water. *Fluoride.* 2006. 39:3-10	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Sabour, S.,Ghorbani, Z.. Developmental fluoride neurotoxicity: clinical importance versus statistical significance. *Environ Health Perspect.* 2013. 121:A70	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Spittle, B.. Fluoride toxicity and donkeys. *Fluoride.* 2010. 43:4	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation

Level	Bibliography	Reason for Exclusion
L2	Spittle, B.. Halting the inertia of indifference: Fluoride and fertility revisited. *Fluoride.* 2009. 42:159-161	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation

Supplementary Material 6. In vitro evidence

This supplement provides details of the search strategies for multiple bibliographic databases, with resulting eligible reviews of in vitro evidence. High-level search concepts and specific database search terms for Medline OVID, MEDLINE, Embase, and PubMed are described. To supplement the description of *in* vitro evidence in the main manuscript, a longer summary is included here.

6.1. Literature search for in vitro evidence

Strategy

Search Question	**Are there any health risks due to fluoride exposure?**	
Major Concepts	1. Fluoride 2. Outcomes: cancer, immunotoxicity, genotoxicity and all other potential adverse effects	
Search Terms	**Concept 1**	**Concept 2**
	Fluorides, fluorine, flurine, fluride, fluoridation	Mechanism of action, mode of action, cancer, immunotoxicity, genotoxicity, toxicokinetics, pharmacokinetics

Trial Ex. 131.1393

6.2. Bibliographic database search terms and output for in vitro studies

Medline Ovid

Concept	#	Medline query
Fluoride	1	exp Fluorides/
	2	exp Fluoridation/
	3	fluorid*.tw.
	4	fluorin*.tw.
	5	flurin*.tw.
	6	flurid*.tw.
	7	or/1-6
Outcomes	8	Mechanism of action.mp.
	9	(mechanism* adj3 action*).tw.
	10	mode of action.mp.
	11	(mode* adj3 action*).tw.
	12	exp Adverse Outcome Pathways/
	13	exp Toxicity Tests/
	14	(toxic* adj3 test*).tw.
	15	exp Animal Testing Alternatives/
	16	(toxic* adj3 test*).tw.
	17	Molecular initiating events.mp.
	18	exp In Vitro Techniques/
	19	in vitro testing.mp.

Concept	#	Medline query
	20	in vitro test*.mp.
	21	Structure-Activity Relationship/
	22	structure activity relationship*.tw.
	23	exp Pharmacokinetics/
	24	pharmacokinetic*.tw.
	25	toxicokinetics/
	26	toxicokinetic*.tw.
	27	exp Neoplasms/
	28	neoplas*.tw.
	29	cancer*.tw.
	30	malignan*.tw.
	31	tumor*.tw.
	32	tumour*.tw.
	33	sarcoma*.tw.
	34	carcinoma*.tw.
	35	Mutagens/
	36	Mutagenicity Tests/
	37	mutagen*.tw.
	38	Mutation/
	39	mutation*.tw.
	40	genotox*.tw.
	41	Toxicogenetics/

Concept	#	Medline query
	42	toxicogenetic*.tw.
	43	micronucle*.tw.
	44	electrophil*.tw.
	45	Carcinogenesis/
	46	carcinogen*.tw.
	47	DNA Damage/
	48	(dna adj3 damage*).tw.
	49	Oxidative Stress/
	50	oxidative stress.tw.
	51	epigenetic*.tw.
	52	Genomic Instability/
	53	(gen* adj3 instabilit*).tw.
	54	DNA Repair/
	55	(dna adj3 repair).tw.
	56	chronic inflamm*.tw.
	57	immortaliz*.tw.
	58	Immunosuppressive Agents/
	59	(immunosuppressi* adj3 agent*).tw.
	60	receptor mediated effect*.tw.
	61	Cell Transformation, Neoplastic/
	62	(cell* adj3 transformation*).tw.
	63	Cell Proliferation/

Concept	#	Medline query
	64	(cell* adj3 proliferation*).tw.
	65	Cell Death/
	66	(cell* adj3 death*).tw.
	67	SAR.tw.
	68	ADME.tw.
	69	or/8-68
Fluoride + outcomes	70	7 and 69
2006 - current	71	limit 70 to yr="2006 -Current"

EMBASE

Concept	#	EMBASE query
Fluoride	1	exp fluoride/
	2	exp fluoridation/
	3	fluorid*.tw.
	4	flurid*.tw.
	5	fluorin*.tw.
	6	flurin*.tw.
	7	or/1-6
Outcomes	8	exp adverse outcome pathway/
	9	exp toxicity testing/
	10	exp animal testing alternative/
	11	exp in vitro study/
	12	exp structure activity relation/
	13	exp pharmacokinetics/
	14	toxicokinetics/
	15	exp neoplasm/
	16	exp malignant neoplasm/
	17	neoplas*.tw.
	18	cancer*.tw.
	19	malignan*.tw.
	20	carcino*.tw.
	21	sarco*.tw.

1398

Concept	#	EMBASE query
	22	tumor*.tw.
	23	tumour*.tw.
	24	exp mutagenic agent/
	25	(mutagen* adj3 agen*).tw.
	26	exp mutagen testing/
	27	(mutagen* adj3 test*).tw.
	28	exp mutation/
	29	mutation*.tw.
	30	exp gene mutation/
	31	(gene* adj3 mutation*).tw.
	32	exp genotoxicity/
	33	exp genotoxicity assay/
	34	genotox*.tw.
	35	exp toxicogenetics/
	36	toxicogen*.tw.
	37	carcinogenesis/
	38	(cancer* adj3 induction).tw.
	39	(cancer* adj3 theor*).tw.
	40	cancerogen.tw.
	41	neoplasmogen.tw.
	42	oncogen.tw.
	43	tumorigen.tw.

Concept	#	EMBASE query
	44	tumourigen.tw.
	45	(tumor* adj3 formation).tw.
	46	(tumour* adj3 formation).tw.
	47	(tumor* adj3 genesis).tw.
	48	(tumour* adj3 genesis).tw.
	49	(tumor* adj3 induction).tw.
	50	(tumour* adj3 induction).tw.
	51	exp micronucleus/
	52	micronucle*.tw.
	53	exp DNA damage/
	54	(dna adj3 damag*).tw.
	55	(dna adj3 break*).tw.
	56	(dna adj3 lesion*).tw.
	57	(dna adj3 fragment*).tw.
	58	exp DNA repair/
	59	(dna adj3 repair*).tw.
	60	(gen* adj3 repair*).tw.
	61	exp chromosome aberration/
	62	(chromosom* adj3 aberration*).tw.
	63	(chromosom* adj3 anomal*).tw.
	64	(chromosom* adj3 abnormal*).tw.
	65	(chromosom* adj3 defect*).tw.

Concept	#	EMBASE query
	66	(chromosom* adj3 error*).tw.
	67	exp oxidative stress/
	68	oxidative stress*.tw.
	69	exp electrophilic stress/
	70	electrophil* stress*.tw.
	71	exp epigenetics/
	72	epigenetic*.tw.
	73	exp cell transformation/
	74	(cell* adj3 transformation*).tw.
	75	exp cell proliferation/
	76	(cell* adj3 proliferat*).tw.
	77	exp cell death/
	78	(cell* adj3 death).tw.
	79	(cell* adj3 necrosis).tw.
	80	(cell* adj3 aging).tw.
	81	(cell* adj3 degeneration).tw.
	82	(cell* adj3 survival).tw.
	83	(gene* adj3 transformation*).tw.
	84	genomic instability/
	85	gen* instabilit*.tw.
	86	genetic stability/
	87	(gen* adj3 stabilit*).tw.

Concept	#	EMBASE query
	88	(gen* adj3 damag*).tw.
	89	exp chronic inflammation/
	90	chronic inflammat*.tw.
	91	or/8-90
Fluoride + outcomes	92	7 and 91
2006 - current	93	limit 92 to yr="2006 -Current"

PubMed

Concept	#	Pubmed query	Results
Fluoride	1	(((fluoride[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word]	97522
Mechanistic	2	((((((((((((adverse outcome pathways[MeSH Terms]) OR adverse outcome pathway*[Text Word]) OR toxicity test[MeSH Terms]) OR toxicity test*[Text Word]) OR animal testing alternatives[MeSH Terms]) OR animal testing alternative*[Text Word]) OR in vitro[MeSH Terms]) OR in vitro stud*[Text Word]) OR in vitro test*[Text Word]) OR structure activity relationships[MeSH Terms]) OR structure activity relationship*[Text Word]) OR pharmacokinetics[MeSH Terms]) OR pharmacokinetic*[Text Word]) OR toxicokinetics[MeSH Terms]) OR toxicokinetic*[Text Word]	
Cancer	3	((((((((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word])	

Concept	#	Pubmed query	Results
		OR tumors[MeSH Terms]) OR tumor*[Text Word]) OR tumours[MeSH Terms]) OR tumour*[Text Word]) OR oncogenesis[MeSH Terms]) OR oncogens[MeSH Terms]) OR oncogen*[Text Word]) OR carcinogenesis tests[MeSH Terms]) OR carcinogens[MeSH Terms]) OR tumor* formation*[Text Word]) OR tumour* formation*[Text Word]) OR tumor* genesis[Text Word]) OR tumour* genesis) OR cancer induction[MeSH Terms]) OR cancer* induction[Text Word]) OR induction cancer*) OR cancer* theor*[Text Word]	
Genotoxicity	4	((genotoxicity tests[MeSH Terms]) OR genotoxicant induced micronuclei[MeSH Terms]) OR genotoxic stresses[MeSH Terms]) OR genotoxins[MeSH Terms]) OR genotox*[Text Word]) OR micronucleus assays[MeSH Terms]) OR micronucle* assa*[Text Word]) OR dna damage[MeSH Terms]) OR dna damag*[Text Word]) OR dna break[MeSH Terms]) OR dna break*[Text Word]) OR dna lesion*[Text Word]) OR dna fragmentation[MeSH Terms]) OR dna fragment*[Text Word]) OR dna repair[MeSH Terms])	

Concept	#	Pubmed query	Results
		OR dna repair*[Text Word]) OR chromosome aberration[MeSH Terms]) OR chromosom* aberration*[Text Word]) OR chromosom* anomal*[Text Word]) OR chromosome abnormality[MeSH Terms]) OR chromosom* abnormal*[Text Word]) OR chromosome defective micronucleus[MeSH Terms]) OR chromosom* defect*[Text Word]) OR chromosom* error*[Text Word]) OR oxidative stress[MeSH Terms]) OR oxidative stress*[Text Word]) OR electrophilic stress*[Text Word]) OR cell transformation, neoplastic[MeSH Terms]) OR cell* transformation*[Text Word]) OR cell proliferation[MeSH Terms]) OR cell* proliferation*[Text Word]) OR cell aging[MeSH Terms]) OR cell* aging[Text Word]) OR cell* degeneration*[Text Word]) OR cell death[MeSH Terms]) OR cell* death*[Text Word]) OR cell* necros*[Text Word]) OR cell survival[MeSH Terms]) OR cell* survival[Text Word]) OR epigenetic[MeSH Terms]) OR epigenetic process[MeSH Terms]) OR epigenomic[MeSH Terms]) OR epigen*[Text Word])	

Concept	#	Pubmed query	Results
		OR genomic stability[MeSH Terms]) OR genomic instability[MeSH Terms]) OR genomic stabilit*[Text Word]) OR genomic instabilit*[Text Word]) OR genom* stabilit*[Text Word]) OR genom* instabilit*[Text Word]) OR chronic inflammation[MeSH Terms]) OR chronic inflammat*[Text Word]	
Outcomes, all	5	earch ((((((((((((((((adverse outcome pathways[MeSH Terms]) OR adverse outcome pathway*[Text Word]) OR toxicity test[MeSH Terms]) OR toxicity test*[Text Word]) OR animal testing alternatives[MeSH Terms]) OR animal testing alternative*[Text Word]) OR in vitro[MeSH Terms]) OR in vitro stud*[Text Word]) OR in vitro test*[Text Word]) OR structure activity relationships[MeSH Terms]) OR structure activity relationship*[Text Word]) OR pharmacokinetics[MeSH Terms]) OR pharmacokinetic*[Text Word]) OR toxicokinetics[MeSH Terms]) OR toxicokinetic*[Text Word])) OR ((((((((((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word])	1580398

Concept	#	Pubmed query	Results
		OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumors[MeSH Terms]) OR tumor*[Text Word]) OR tumours[MeSH Terms]) OR tumour*[Text Word]) OR oncogenesis[MeSH Terms]) OR oncogens[MeSH Terms]) OR oncogen*[Text Word]) OR carcinogenesis tests[MeSH Terms]) OR carcinogens[MeSH Terms]) OR tumor* formation*[Text Word]) OR tumour* formation*[Text Word]) OR tumor* genesis[Text Word]) OR tumour* genesis) OR cancer induction[MeSH Terms]) OR cancer* induction[Text Word]) OR induction cancer*) OR cancer* theor*[Text Word])) OR (((genotoxicity tests[MeSH Terms]) OR genotoxicant induced micronuclei[MeSH Terms]) OR genotoxic stresses[MeSH Terms]) OR genotoxins[MeSH Terms]) OR genotox*[Text Word]) OR micronucleus assays[MeSH Terms]) OR micronucle* assa*[Text Word]) OR dna damage[MeSH Terms]) OR dna damag*[Text Word]) OR dna break[MeSH Terms])	

Concept	#	Pubmed query	Results
		OR dna break*[Text Word]) OR dna lesion*[Text Word]) OR dna fragmentation[MeSH Terms]) OR dna fragment*[Text Word]) OR dna repair[MeSH Terms]) OR dna repair*[Text Word]) OR chromosome aberration[MeSH Terms]) OR chromosom* aberration*[Text Word]) OR chromosom* anomal*[Text Word]) OR chromosome abnormality[MeSH Terms]) OR chromosom* abnormal*[Text Word]) OR chromosome defective micronucleus[MeSH Terms]) OR chromosom* defect*[Text Word]) OR chromosom* error*[Text Word]) OR oxidative stress[MeSH Terms]) OR oxidative stress*[Text Word]) OR electrophilic stress*[Text Word]) OR cell transformation, neoplastic[MeSH Terms]) OR cell* transformation*[Text Word]) OR cell proliferation[MeSH Terms]) OR cell* proliferation*[Text Word]) OR cell aging[MeSH Terms]) OR cell* aging[Text Word]) OR cell* degeneration*[Text Word]) OR cell death[MeSH Terms]) OR cell* death*[Text Word]) OR cell* necros*[Text Word]) OR cell survival[MeSH Terms])	
1408			

Concept	#	Pubmed query	Results
		OR cell* survival[Text Word]) OR epigenetic[MeSH Terms]) OR epigenetic process[MeSH Terms]) OR epigenomic[MeSH Terms]) OR epigen*[Text Word]) OR genomic stability[MeSH Terms]) OR genomic instability[MeSH Terms]) OR genomic stabilit*[Text Word]) OR genomic instabilit*[Text Word]) OR genom* stabilit*[Text Word]) OR genom* instabilit*[Text Word]) OR chronic inflammation[MeSH Terms]) OR chronic inflammat*[Text Word])	
Fluoride + outcomes (all)	6	Search (((((fluoride[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word])) AND ((((((((((((((((adverse outcome pathways[MeSH Terms]) OR adverse outcome pathway*[Text Word]) OR toxicity test[MeSH Terms]) OR toxicity test*[Text Word]) OR animal testing alternatives[MeSH Terms]) OR animal testing alternative*[Text Word]) OR in vitro[MeSH Terms]) OR in vitro stud*[Text Word]) OR in vitro test*[Text Word]) OR structure activity relationships[MeSH Terms]) OR structure activity relationship*[Text Word]) OR pharmacokinetics[MeSH Terms]) OR	12181

Concept	#	Pubmed query	Results
		pharmacokinetic*[Text Word]) OR toxicokinetics[MeSH Terms]) OR toxicokinetic*[Text Word])) OR (((((((((((((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumors[MeSH Terms]) OR tumor*[Text Word]) OR tumours[MeSH Terms]) OR tumour*[Text Word]) OR oncogenesis[MeSH Terms]) OR oncogens[MeSH Terms]) OR oncogen*[Text Word]) OR carcinogenesis tests[MeSH Terms]) OR carcinogens[MeSH Terms]) OR tumor* formation*[Text Word]) OR tumour* formation*[Text Word]) OR tumor* genesis[Text Word]) OR tumour* genesis) OR cancer induction[MeSH Terms]) OR cancer* induction[Text Word]) OR induction cancer*) OR cancer* theor*[Text Word])) OR ((genotoxicity tests[MeSH Terms]) OR genotoxicant induced micronuclei[MeSH Terms]) OR genotoxic	

Concept	#	Pubmed query	Results
		stresses[MeSH Terms]) OR genotoxins[MeSH Terms]) OR genotox*[Text Word]) OR micronucleus assays[MeSH Terms]) OR micronucle* assa*[Text Word]) OR dna damage[MeSH Terms]) OR dna damag*[Text Word]) OR dna break[MeSH Terms]) OR dna break*[Text Word]) OR dna lesion*[Text Word]) OR dna fragmentation[MeSH Terms]) OR dna fragment*[Text Word]) OR dna repair[MeSH Terms]) OR dna repair*[Text Word]) OR chromosome aberration[MeSH Terms]) OR chromosom* aberration*[Text Word]) OR chromosom* anomal*[Text Word]) OR chromosome abnormality[MeSH Terms]) OR chromosom* abnormal*[Text Word]) OR chromosome defective micronucleus[MeSH Terms]) OR chromosom* defect*[Text Word]) OR chromosom* error*[Text Word]) OR oxidative stress[MeSH Terms]) OR oxidative stress*[Text Word]) OR electrophilic stress*[Text Word]) OR cell transformation, neoplastic[MeSH Terms]) OR cell* transformation*[Text Word]) OR cell proliferation[MeSH Terms]) OR cell*	
	1411		

Concept	#	Pubmed query	Results
		proliferation*[Text Word]) OR cell aging[MeSH Terms]) OR cell* aging[Text Word]) OR cell* degeneration*[Text Word]) OR cell death[MeSH Terms]) OR cell* death*[Text Word]) OR cell* necros*[Text Word]) OR cell survival[MeSH Terms]) OR cell* survival[Text Word]) OR epigenetic[MeSH Terms]) OR epigenetic process[MeSH Terms]) OR epigenomic[MeSH Terms]) OR epigen*[Text Word]) OR genomic stability[MeSH Terms]) OR genomic instability[MeSH Terms]) OR genomic stabilit*[Text Word]) OR genomic instabilit*[Text Word]) OR genom* stabilit*[Text Word]) OR genom* instabilit*[Text Word]) OR chronic inflammation[MeSH Terms]) OR chronic inflammat*[Text Word]))	
2006 - current	7	Search ((((((fluoride[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word])) AND ((((((((((((((((adverse outcome pathways[MeSH Terms]) OR adverse outcome pathway*[Text Word]) OR toxicity test[MeSH Terms]) OR toxicity test*[Text Word]) OR animal testing alternatives[MeSH Terms]) OR animal testing	5026

Concept	#	Pubmed query	Results
		alternative*[Text Word]) OR in vitro[MeSH Terms]) OR in vitro stud*[Text Word]) OR in vitro test*[Text Word]) OR structure activity relationships[MeSH Terms]) OR structure activity relationship*[Text Word]) OR pharmacokinetics[MeSH Terms]) OR pharmacokinetic*[Text Word]) OR toxicokinetics[MeSH Terms]) OR toxicokinetic*[Text Word])) OR ((((((((((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumors[MeSH Terms]) OR tumor*[Text Word]) OR tumours[MeSH Terms]) OR tumour*[Text Word]) OR oncogenesis[MeSH Terms]) OR oncogens[MeSH Terms]) OR oncogen*[Text Word]) OR carcinogenesis tests[MeSH Terms]) OR carcinogens[MeSH Terms]) OR tumor* formation*[Text Word]) OR tumour* formation*[Text Word]) OR tumor* genesis[Text Word]) OR tumour* genesis) OR cancer induction[MeSH Terms]) OR	
1413			

Concept	#	Pubmed query	Results
		cancer* induction[Text Word]) OR induction cancer*) OR cancer* theor*[Text Word])) OR (((genotoxicity tests[MeSH Terms]) OR genotoxicant induced micronuclei[MeSH Terms]) OR genotoxic stresses[MeSH Terms]) OR genotoxins[MeSH Terms]) OR genotox*[Text Word]) OR micronucleus assays[MeSH Terms]) OR micronucle* assa*[Text Word]) OR dna damage[MeSH Terms]) OR dna damag*[Text Word]) OR dna break[MeSH Terms]) OR dna break*[Text Word]) OR dna lesion*[Text Word]) OR dna fragmentation[MeSH Terms]) OR dna fragment*[Text Word]) OR dna repair[MeSH Terms]) OR dna repair*[Text Word]) OR chromosome aberration[MeSH Terms]) OR chromosom* aberration*[Text Word]) OR chromosom* anomal*[Text Word]) OR chromosome abnormality[MeSH Terms]) OR chromosom* abnormal*[Text Word]) OR chromosome defective micronucleus[MeSH Terms]) OR chromosom* defect*[Text Word]) OR chromosom* error*[Text Word]) OR oxidative stress[MeSH Terms]) OR	

Concept	#	Pubmed query	Results
		oxidative stress*[Text Word]) OR electrophilic stress*[Text Word]) OR cell transformation, neoplastic[MeSH Terms]) OR cell* transformation*[Text Word]) OR cell proliferation[MeSH Terms]) OR cell* proliferation*[Text Word]) OR cell aging[MeSH Terms]) OR cell* aging[Text Word]) OR cell* degeneration*[Text Word]) OR cell death[MeSH Terms]) OR cell* death*[Text Word]) OR cell* necros*[Text Word]) OR cell survival[MeSH Terms]) OR cell* survival[Text Word]) OR epigenetic[MeSH Terms]) OR epigenetic process[MeSH Terms]) OR epigenomic[MeSH Terms]) OR epigen*[Text Word]) OR genomic stability[MeSH Terms]) OR genomic instability[MeSH Terms]) OR genomic stabilit*[Text Word]) OR genomic instabilit*[Text Word]) OR genom* stabilit*[Text Word]) OR genom* instabilit*[Text Word]) OR chronic inflammation[MeSH Terms]) OR chronic inflammat*[Text Word]))) AND ("2006"[Date - Publication] : "2020"[Date - Publication])	

Concept	#	Pubmed query	Results
Rev /SR /MA /CR	8	Search (((((((fluoride[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word])) AND ((((((((((((((((adverse outcome pathways[MeSH Terms]) OR adverse outcome pathway*[Text Word]) OR toxicity test[MeSH Terms]) OR toxicity test*[Text Word]) OR animal testing alternatives[MeSH Terms]) OR animal testing alternative*[Text Word]) OR in vitro[MeSH Terms]) OR in vitro stud*[Text Word]) OR in vitro test*[Text Word]) OR structure activity relationships[MeSH Terms]) OR structure activity relationship*[Text Word]) OR pharmacokinetics[MeSH Terms]) OR pharmacokinetic*[Text Word]) OR toxicokinetics[MeSH Terms]) OR toxicokinetic*[Text Word])) OR ((((((((((((((((((((((((cancer[MeSH Terms]) OR cancer*[Text Word]) OR neoplasm[MeSH Terms]) OR neoplas*[Text Word]) OR malignancy[MeSH Terms]) OR malignan*[Text Word]) OR carcinoma[MeSH Terms]) OR carcino*[Text Word]) OR sarcoma[MeSH Terms]) OR sarco*[Text Word]) OR tumors[MeSH Terms]) OR tumor*[Text Word]) OR tumours[MeSH Terms]) OR	248

Concept	#	Pubmed query	Results
		tumour*[Text Word]) OR oncogenesis[MeSH Terms]) OR oncogens[MeSH Terms]) OR oncogen*[Text Word]) OR carcinogenesis tests[MeSH Terms]) OR carcinogens[MeSH Terms]) OR tumor* formation*[Text Word]) OR tumour* formation*[Text Word]) OR tumor* genesis[Text Word]) OR tumour* genesis) OR cancer induction[MeSH Terms]) OR cancer* induction[Text Word]) OR induction cancer*) OR cancer* theor*[Text Word])) OR ((genotoxicity tests[MeSH Terms]) OR genotoxicant induced micronuclei[MeSH Terms]) OR genotoxic stresses[MeSH Terms]) OR genotoxins[MeSH Terms]) OR genotox*[Text Word]) OR micronucleus assays[MeSH Terms]) OR micronucle* assa*[Text Word]) OR dna damage[MeSH Terms]) OR dna damag*[Text Word]) OR dna break[MeSH Terms]) OR dna break*[Text Word]) OR dna lesion*[Text Word]) OR dna fragmentation[MeSH Terms]) OR dna fragment*[Text Word]) OR dna repair[MeSH Terms]) OR dna repair*[Text Word]) OR chromosome aberration[MeSH Terms]) OR chromosom*	

Concept	#	Pubmed query	Results
		aberration*[Text Word]) OR chromosom* anomal*[Text Word]) OR chromosome abnormality[MeSH Terms]) OR chromosom* abnormal*[Text Word]) OR chromosome defective micronucleus[MeSH Terms]) OR chromosom* defect*[Text Word]) OR chromosom* error*[Text Word]) OR oxidative stress[MeSH Terms]) OR oxidative stress*[Text Word]) OR electrophilic stress*[Text Word]) OR cell transformation, neoplastic[MeSH Terms]) OR cell* transformation*[Text Word]) OR cell proliferation[MeSH Terms]) OR cell* proliferation*[Text Word]) OR cell aging[MeSH Terms]) OR cell* aging[Text Word]) OR cell* degeneration*[Text Word]) OR cell death[MeSH Terms]) OR cell* death*[Text Word]) OR cell* necros*[Text Word]) OR cell survival[MeSH Terms]) OR cell* survival[Text Word]) OR epigenetic[MeSH Terms]) OR epigenetic process[MeSH Terms]) OR epigenomic[MeSH Terms]) OR epigen*[Text Word]) OR genomic stability[MeSH Terms]) OR genomic instability[MeSH Terms]) OR genomic stabilit*[Text	

Concept	#	Pubmed query	Results
		Word]) OR genomic instabilit*[Text Word]) OR genom* stabilit*[Text Word]) OR genom* instabilit*[Text Word]) OR chronic inflammation[MeSH Terms]) OR chronic inflammat*[Text Word]))) AND ("2006"[Date - Publication] : "2020"[Date - Publication])) AND (((((("meta analysis"[Publication Type]) OR "systematic review"[Publication Type]) OR "review"[Publication Type]) OR "scientific integrity review"[Publication Type]) OR "guideline"[Publication Type])	

6.3. Summary of in vitro evidence

Evidence from in vitro models of humans and non-human animals

Data abstraction from original in vitro studies is not considered; however, literature reviews covering original studies investigating fluoride induced toxicity in various in vitro models would be reviewed and summarized, for weight of evidence assessment along with animal and human data. The current review examined in vitro studies to understand the mechanisms of action of fluoride in exposed animals or humans. The evidence collected from literature reviews on this subject was discussed by type of mechanism, and we summarized concentration ranges in which fluoride induced a positive effect, e.g., oxidative stress apoptosis, ER-stress pathway activation, [Ca^{2+}] increase etc.

Characteristics of studies on oxidative stress

As described, "[o]xidative stress is a recognized mode of action of fluoride exposure that has been observed in vitro in several types of cells and also in vivo in soft tissues such as the liver, kidney, brain, lung, and testes in animals and in people living in areas of endemic fluorosis" [350]. Reactive Oxygen species (ROS) can be generated from a variety of sources classified as exogenous and endogenous; UV irradiation, ozone and polyaromatic hydrocarbons (PAH) are key examples for exogenous sources. There are multiple sources considered as endogenous such as mitochondrial oxidative phosphorylation, xenobiotic metabolism, active peroxisomes and inflammation.

Numerous studies demonstrated that one of the downstream effects of increase in release of ROS and subsequent oxidative stress is induction of cytotoxicity by activating apoptotic pathways. At cellular level, fluoride appeared to induce oxidative stress, cell cycle arrest, and apoptosis through various pathways such as inhibition of metalloproteins, organelle disruption, altered pH, and electrolyte imbalance. For example, excess NaF (up to 3 mM) showed to cause DNA damage, oxidative stress, mitochondrial agglutination and cytoskeleton damage to neuronal cell lines [351]. Several in vitro studies that demonstrated oxidative stress upon fluoride exposure were identified by searching through published review studies on this association and are summarized in Table 4. In summary, based on these studies, fluoride

(mostly as NaF salt) caused cytotoxicity or another apical endpoint via induction of oxidative stress pathway (measured as ROS levels, SOD activity, LDH release etc.) in a range of cell lines at concentrations ranging between 0.005 mM and 6 mM. These concentrations may be compared to human plasma fluoride levels.

Table 4: Characteristics of studies on oxidative stress

Reference	Cellular system	Fluoride Exposure	Endpoints assessed (positive effect)
Chen L 2017 [352]	Neuro-2A (mouse neuroblastoma cell line)	1 – 6 mM	Cell viability Lactate dehydrogenase (LDH) release
Zhang 2015 [353]	PC 12 cells (pheochromocytoma cells)	0.005 mM	Intracellular ROS increase Apoptotic cells Cytotoxicity
Chen R 2017 [354]	BV-2 microglia cells	0.5 - 2 mM	Increase of IL-6 concentration Decrease of cell viability Decrease in SOD activity Increase of TNF-α level
Shuhua 2012 [355]	BV-2 microglia cells	0.024 mM	SOD activities decreased NOS (synthesizing NO) increased
Xu 2013 [356]	Human neuroblastoma SH-SY5 Y cells	0.48 - 0.95 mM	LDH levels higher
Ma 2017 [357]	Human umbilical vein endothelial cells (HUVECs)	0, 4.2, and 8.4 mg/L	Oxidative stress and impaired NO production are involved in their pro-inflammatory and pro-apoptotic effects.
Grzegorzewska 2020 [358]	Chicken embryonic gonads	75, 150, 300, and 600 mg/L	Increased expression of antioxidant enzymes (CAT and SOD) and nuclear respiratory factors (Nrfs)

Reference	Cellular system	Fluoride Exposure	Endpoints assessed (positive effect)
Peng 2019 [359]	F9 embryonic carcinoma cells	0, 40, 80, and 160 mg/L	Decreased Sirtuin 1 (Sirt1) protein expression, promoted the acetylation of manganese superoxide dismutase (SOD2), increased mitochondrial reactive oxygen species (mROS) production, and stimulated cytotoxicity
García-Montalvo 2009 [164]	Mouse pancreatic beta-cells (betaTC-6)	0.15 , 0.4, 3, 20, and 40 mg/L	Decreased SOD activity, in a dose-dependent manner, increase in the generation of O(2)(-), and decreased mitochondrial membrane potential
Zhang 2007 [360]	Primary rat hippocampal neurons	20, 40, and 80 mg/L	Increased malondialdehyde levels, decreased glutathione levels and glutathione peroxidase activities, reduced superoxide dismutase activity
Gao 2008 [361]	Neuroblastoma (SH-SY5Y) cells	1 to 100 mg/L	Lipid peroxidation and protein oxidation in a dose-response manner

Characteristics of studies on apoptosis

Apoptosis is genetically programmed cell death, an irreversible process of cell senescence with characteristic features different from other cellular mechanisms of death such as necrosis. There are three pathways related to fluoride exposure induced apoptosis: mitochondrion-mediated, endoplasmic reticulum (ER) stress-mediated, and death receptor-mediated pathways [350, 362-366].

Characteristics of studies on mitochondrial dysfunction

Mitochondrial dysfunction has been shown to contribute to the occurrence of apoptosis and it is central to the apoptotic pathway [367]. There are three key types of proteins involving in this pathway: Bcl-2 family proteins, caspases, and mitochondrial pro-apoptosis proteins a rising level of intracellular reactive oxygen species (ROS), as a signal of oxidative stress, can also activate the apoptosis signaling pathway Mitochondrion is both a target of ROS and a source of the additional ROS generation [365].

Evidence show that fluoride exposure induces apoptosis by regulating the mitochondrial pathway (decreased MMP and increased ROS) in H9C2 cardiomyocytes [368], human thyroid cells [369], and umbilical vein endothelial cells [357]. Fluoride exposure can trigger apoptosis via increasing mRNA or protein levels of Cyt c, caspase-3, and caspase-9 in HL-60 cells [370], Leydig cells [371], H9C2 cardiomyocytes [372], and human lung BEAS- 2B cells [373]. Another study found that fluoride induced cell apoptosis is accompanied by increased Bax mRNA expression level and reduced Bcl-2 expression level in PC12 cell [335]. More details are provided in Table 5.

Table 5: Characteristics of studies on mitochondrial dysfunction

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Yan et al., 2015 [368]	H9c2	0, 2, 4, 8, and 16 mg/L	Induced apoptosis by increasing intracellular reactive oxygen species and downregulating mitochondrial membrane potential
Liu et al., 2014 [369]	human thyroid cells (Nthy-ori 3-1)	0, 0.4, 4.2, and 12.6 mg/L	Decreased cell viability improves the lactate dehydrogenase leakage rate, and reactive oxygen species level.
Ma et al., 2017 [357]	human umbilical vein endothelial cells (HUVECs)	0, 4.2, and 8.4 mg/L	Induced endothelial activation and apoptosis. Oxidative stress and impaired NO production are involved in their pro-inflammatory and pro-apoptotic effects.

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Anuradha et al., 2001 [370]	HL-60	8.4 mg/L	Induced apoptosis by oxidative stress-induced lipid peroxidation, causing loss of deltaPsi(m), and thereby releasing cytochrome c into the cytosol and further triggering the caspase cascade.
Song et al., 2014 [371]	Leydig cells	0, 5, 10, and 20 mg/L	Increased expression levels of stress response factors, signal transduction components, and apoptosis-related proteins, including caspase-3/caspase-9, B-cell lymphoma 2 (Bcl-2), and Bax
Yan et al., 2017 [372]	H9c2	0, 5, 10, 20, and 40 mg/L	Increased mRNA levels of caspase-3, caspase-9, and cytochrome c. Induced apoptosis through the mitochondrial pathway.
Ying et al., 2017 [373].	human lung BEAS-2B	0, 1, 2.1, 4.2, 8.4, and 16.8 mg/L	Induced apoptosis through mitochondria-mediated signal pathways. Increased bax, caspase-3, caspase-9, p53, and the cytoplasmic CytC, decreased bcl-2 and mitochondrial CytC. Increased ROS and decreased membrane potential of mitochondria.
Liao et al., 2017 [335]	PC12	0, 2.1, and 21 mg/L	Decreased cell activity, enhanced cell apoptosis, increased c-fos, CAMKII, and Bax mRNA expression. Decreased Bcl-2 expression.

Characteristics of studies on endoplasmic reticulum dysfunction

The endoplasmic reticulum is the main site for the folding and maturation of transmembrane, secretory, and ER-resident proteins. Accumulation of misfolded and unfolded proteins will cause ER stress, leading to the activation of self-protecting mechanisms called unfolded protein response (UPR). UPR is responsible for either relieving ER stress or inducing apoptosis [374, 375].

As shown in Table 6, Fluoride exposure could induce apoptosis by triggering ER stress through upregulated GRP78, PERK, phosphorylation-eukaryotic initiation factor 2α (p-eIF2α), and CHOP in Sertoli cells [319] and human thyroid follicular epithelial cells [369]. Studies on mouse ameloblast-derived LS8 cells showed that fluoride exposure could induce caspase-dependent apoptosis through overexpression of PERK, eIF2α, IRE1, activation of Xbp-1, BiP/GRP78, GADD153/CHOP, and JNK, which in turn inducing ER stress and UPR [376, 377].

Table 6: Characteristics of studies on endoplasmic reticulum dysfunction

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Yang et al., 2015 [319]	Sertoli cells	0, 6, 12 and 24 mg/L	Decreased cell viability and induced apoptosis. Increased ER stress by up-regulating glucose-regulated protein 78 kDa (GRP78), PKR-like ER kinase (PERK), phosphorylation of eukaryotic translation initiation factor 2α (p-eIF2α) and CCAAT/enhancer-binding protein-homologous protein (CHOP)
Liu et al., 2014 [369]	human thyroid cells (Nthy-ori 3-1)	0, 4.2 mg/L	Induced cytotoxicity related to IRE1 pathway-induced apoptosis.
Sharma et al., 2008 [376]	ameloblast-derived LS8	0, 5.1, 10.5, 21, and 42 mg/L	Induced ER stress response interfering with protein synthesis and secretion. Extracellular secretion of SEAP decreased in a linear, dose-dependent manner.
Sharma et al., 2010 [378]	ameloblast-derived LS8	0, 2.1 mg/L	Increased cell stress by phosphorylating stress-related proteins, PERK, eIF2α, JNK and c-jun

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Kubota et al., 2005 [377]	ameloblast-derived LS8	0, 21, 42, 63, and 84 mg/L	Inhibited cell growth at low dose, whereas higher doses induced ER stress and caspase-mediated DNA fragmentation.

Characteristics of studies on death receptor-mediated pathways

Fluoride can induce apoptosis by regulating Fas ligand (FasL)/Fas signaling pathway and tumor necrosis factor-α (TNF-α)/tumor necrosis factor-αrecpter-1 (TNF-R1) signaling pathway, which belongs to the death receptor pathways.

Fluoride exposure could induce apoptosis by upregulating the protein expression of FasL, Fas, caspase-8, caspase-3, and cleaved PARP in the primary rat ameloblasts [379], human neuroblast cells [380], and human gingival fibroblasts [381]. Studies using mice splenic lymphocytes show that fluoride exposure cause ER stress and UPR [382] and decreasing mitochondria transmembrane potential, up-regulating Bax, Bak, Fas, FasL, caspase 9, caspase 8, caspase 7, caspase 6 and caspase 3, and down-regulating Bcl-2 and Bcl-xL [383]. See Table 7 for more details on study characteristics.

Table 7: Characteristics of studies on death receptor-mediated pathways

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Wang et al., 2016 [379]	primary rat ameloblast	0.4, 0.8, 1.6, 3.2, and 6.4 mmol/L	Induced apoptosis via activation of FasL/Fas signaling pathway and diminished secretion of AMBN

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Deng et al., 2016a [382]	mice splenic lymphcytes	0, 4.2, 8.4, and 16.8 mg/L	Induced apoptosis and caused ER stress by up-regulating protein expression levels of glucose-regulated protein 78 (BiP) and glucose-regulated protein 94 (GRP94), and by activating unfolded protein response (UPR).
Deng et al., 2016b [383]	mice splenic lymphcytes	0, 4.2, 8.4, and 16.8 mg/L	Induced apoptosis by decrease of mitochondria transmembrane potential, up-regulation of Bax, Bak, Fas, FasL, caspase 9, caspase 8, caspase 7, caspase 6 and caspase 3 protein expression, and down-regulation of Bcl-2 and Bcl-xL protein expression.
Lee et al., 2008 [381]	human gingival fibroblasts	5, 10, 20, 30, and 40 mmol/L	Induced apoptosis through the Bcl-2 family and death receptor-mediated pathway. Increased cytochrome c release from the mitochondria into the cytosol, enhanced the caspase-9, -8 and -3 activities, the cleavage of poly (ADP-ribose) polymerase (PARP), and up-regulated the voltage-dependent anion channel (VDAC).
Xu et al., 2011 [380]	human neuroblastoma (SH-SY5Y)	0, 20, 40, and 80 mg/L	Induce apoptosis by increasing caspase-3 and mRNA expression levels for Fas, Fas-L, and caspases (-3 and -8).

Characteristics of studies on Na, K-ATPase

Sodium, potassium-activated adenosine triphosphatase (Na, K-ATPase) is a member of the P-type family of active cation transport proteins, which maintains sodium and potassium homeostasis in animal cells by transporting Na+-ions to the outside and K+-ions to the inside of the cell, at the expense of ATP. Na, K-ATPase is responsible for the electrochemical gradient across the plasma membrane and the regulation of the cellular ionic homeostasis. In

addition, Na, K-ATPase activity plays a crucial role in the function of neurotransmitter transporters, which are essential for regulating neurotransmitter signaling and homeostasis. [384, 385].

Fluoride exposure inhibits the activity of Na, K-ATPase through multiple pathways. In summary, fluoride has been shown to upregulate PKC, cAMP, cGMP, NO, Pi, PLA2, AA, PGE2, dopamine, glucose and PTH. The formation of these biomarkers inhibits Na, K-ATPase activity. See more details on study characteristics in Table 8.

Table 8: Characteristics of studies on Na, K-ATPase

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Gutowska et al., 2010 [386]	human monocytic line THP-1	0.4, 1.2, 2.4, 4.0 mg/L	decreased the amount of synthesized cellular ATP and increased formation of ROS and apoptosis in a dose-dependent pattern
Agalakova & Gusev 2012 [387]	rat erythrocytes	0, 4, 20, 80, 400 mg/L	Dose- and time-dependent decline of ATP a, diminishing to extremely low levels within 24h.
Cittanova et al., 2002 [388]	rabbit kidney thick ascending limb cells	0, 40, 200, and 400 mg/L	Depletion of Na-K-ATPase activity and renal mitochondrial dysfunction

Characteristics of studies on inflammatory response

Inflammation is the body's immune system's response to an irritant, e.g., infection or tissue damage. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and initiate tissue repair. Chronic inflammation plays an important role in the development of

chronic conditions, e.g., diabetes, atherosclerosis, cardiovascular disease, allergies, and COPD [350, 362, 363].

Studies have shown that fluoride exposure can promote inflammatory response via increasing oxidative stress and ROS in human umbilical vein endothelial cells (Ma 2017), human monocytic line THP-1 [386], and RAW 264.7 murine macrophage line [389]. Fluoride related phosphorylation of c-Jun NH(2)-terminal kinase (JNK) was involved in the pro-inflammatory response in the MDPC-23 odontoblast-like cells [390] and human ameloblast lineage cells [391]. More details on studies are provided in Table 9.

Table 9: Characteristics of studies on inflammatory response

Reference	Cell lines	Sodium fluoride concentrations	Findings and conclusion
Ma 2017 [357]	human umbilical vein endothelial cells (HUVECs)	0, 4.2, and 8.4 mg/L	Endothelial activation and apoptosis. Oxidative stress and impaired NO production are involved in their pro-inflammatory and pro-apoptotic effects.
De la Fuente 2016 [389]	RAW 264.7 murine macrophage line	5, 10, 25, and 65 mg/L	Increased ROS, redox imbalance, lipid peroxidation, and cytokines Il6 and Mip2
Gutowska 2010 [386]	human monocytic line THP-1	0.4, 1.2, 2.4, 4.0 mg/L	Depleted ATP and increased ROS and apoptosis in a dose-dependent pattern
Karube 2009 [390]	MDPC-23 odontoblast-like cells	200 mg/L	phosphorylation of c-Jun NH(2)-terminal kinase (JNK) and p38, exhibited caspase-3 activation, cleavage of poly(ADP-ribose) polymerase, DNA fragmentation, and an increase in cytoplasmic nucleosomes
Zhang Y 2007 [391]	human ameloblast lineage cells	0.4 mg/L	Decreased MMP-20 protein levels and related to suppression of JNK/c-Jun phosphorylation.
Zhang M 2007 [360]	primary rat hippocampal neurons	20, 40, and 80 mg/L	Induced S-phase cell-cycle arrest, up-regulation of NF-kappaB and DNA damage

Supplementary Material 7. Weight of evidence using Bradford Hill considerations for causality

To supplement the discussion of Bradford Hill considerations, a more detailed discussion of evidence pertaining to each consideration is described for the four endpoints (in addition to dental fluorosis) considered candidates for developing a point of departure: cognitive dysfunction (specifically, reduction in IQ scores in children), thyroid dysfunction, kidney dysfunction, and sex hormone alterations. Tables are included to show cited supporting studies separately for each Bradford Hill consideration.

7.1. Reducing IQ scores

Criterion	Summary of recent evidence
Strength of association	• A study of acceptable quality examined by NHMRC [392] reported a significant negative correlation between IQ and drinking water fluoride levels. A reduction of 6.7, 11.2, 10.2 in performance, verbal and full IQ scores, respectively, was observed per increase in log fluoride values [392]. • Although CADTH did not consider the North American cohort study conducted by Green et al [101] to be of acceptable quality, the study was subsequently assessed by the 2020 [103] and 2022 NTP [104] draft reports as having an overall low risk of bias. This study showed a positive association between higher maternal fluoride intake and reduction in IQ. A reduction of 3.66 points was reported per 1 mg increase in daily maternal intake of fluoride. • The current review identified sixteen new studies [9, 11, 14, 18, 26, 37-40, 53, 54, 72, 78, 83, 85, 90], which provided statistically significant results supporting a positive/possible association of reduced IQ levels in response to increasing exposure to water fluoride. Four studies reported either no association between reduction of IQ scores and

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	drinking water [8, 13, 67, 89], or non-significant frequency differences between urinary fluoride levels [42].
	• Three studies [11, 53, 83] reported that an increment of 0.5 mg/L in water fluoride concentration corresponded to:
	  ○ A 9.3- and a 6.2-point reduction in performance IQ in formula-fed and breastfed children, respectively. Such an association remained significant upon controlling for fetal fluoride exposure [53].
	  ○ A 40% reduction in the odds of having excellent IQ in those exposed to low fluoride levels (0.20-1.40 mg/L) [83].
	  ○ A drop of 2 points in full-scale IQ scores [11].
	• A more recent study [26] that used the same cohort (MIREC) reported an association between children's performance IQ and fluoride exposure during the perinatal period and into early childhood. Such an association was reported to differ between boys and girls across the different exposure periods, though more validation is proposed by the authors.
	• Another recent study [13] examined prenatal fluoride exposure in a small mother-child birth cohort in Spain: Results in boys suggest improved scores in cognitive domains with maternal urinary concentrations.

Consistency	• A total of 15 studies [9, 11, 14, 18, 26, 37-40, 53, 54, 72, 83, 85, 90] identified in the current review, and 1 earlier study [392] of high/acceptable quality concluded a positive association with reduced IQ[xli] levels in children/adolescents. • One study [78] identified in the current review concluded a possible positive association, and 1 study [42] reported a non-significant association with reducing IQ scores. • Four studies [8, 13, 67, 89] identified in the current review and 3 earlier [393-395] studies of high/acceptable quality reported no association.

[xli] IQ: involving scores of different IQ tests, or the use of proxies to IQ such as school performance, school tests

	• Within the 16 studies identified in the current review and showing a positive/possible association, the directionality of association did not differ by study design (12 studies were cross-sectional, and 4 were cohorts), geographic location (6 in China, 3 in India, 2 in each of Canada and Mexico, and 1 in each of Indonesia, Pakistan, and Sudan), studied population (12 studies in children and/or adolescents, 4 in mother-child pairs and 1 that examined patients of all ages), or sampling time-frame.
Specificity	Fluoride appears to play a role in the induction of a range of adverse health outcomes, and reduction in IQ levels can be caused by a number of risk factors including exposure to toxic factors other than fluoride.
Temporality	Out of those that showed positive or possibly positive association, there were different follow up durations reported in two cohort studies • Four cohort studies [11, 26, 85] reported an association of maternal fluoride exposure and reduced IQ levels in their offspring, where the long follow up period (at ages 1, 4 then at age 6-12) allowed a reasonable assessment of temporality • Another cohort study [53] reported on the association of water fluoride exposure in newborns using breast milk or formula, where IQ was measured at 3-4 years old. • Fourteen studies [42, 54, 72, 78, 83, 90, 392, 9, 14, 18, 37-40] that showed positive or possibly positive association were cross sectional, whereby an inference of causality cannot be concluded.
Biological gradient (exposure-response)	• Seventeen studies [9, 11, 14, 18, 26, 37-40, 53, 54, 72, 78, 83, 85, 90, 392] provided statistically significant exposure-response relationship supporting a positive/possible association between exposure to fluoride and lower IQ levels, with varying categories of exposure (continuous vs. categorical).

	• One study by Wang 2020 [54] reported a change in IQ scores per 1 mg/L increment of water fluoride (continuous) or compared to a reference quartile.
	  ○ Continuous: β= −1.587 (−2.607, −0.568), p-value= 0.002
	  ○ Quartiles: IQ scores, β= (95% CI), p-value
	  ▪ Quartile 1 (≤0.70): reference
	  ▪ Quartile 2 (0.70–1.00): β= −0.506 (−3.764, 2.753), p-value= 0.761
	  ▪ Quartile 3 (1.00–1.90): β= −3.065(−5.636, −0.493), p-value= 0.020
	  ▪ Quartile 4 (> 1.90): β= −3.471(−6.108, −0.835), p-value= 0.010

Biological plausibility	• Fluoride has reportedly been capable of crossing the blood brain barrier with the subsequent accumulation in brain tissues [83]. Animal evidence showed fluoride in excess is capable of reducing the "fluidity of the synaptic membrane of the hippocampus in rats" leading to hippocampal neuronal impairment and neurodegenerative changes, resulting in impaired learning and memory [83]. Such neurologic/cognitive effects are more pronounced in children compared to adults due to the former's relatively less brain capacity to clear the toxicant (fluoride) burden [83]. • Human studies also reported on the possibility of fluoride to cross the placental barrier from the mother to her developing fetus [85], or via breastfeeding to her newborn [53]. • Infants who are fed formula reconstituted with fluoridated water have approximately three to four times greater exposure to fluoride than adults on a per body-weight basis. Formula-fed infants residing in fluoridated areas have an approximate 70-fold higher fluoride intake than exclusively breastfed infants [53] • However, based on the draft 2020 NTP [103] review of evidence on mechanism of action related to fluoride induced neurocognitive effects,

	the available data is “too general” or “cannot necessarily be attributed to effects on learning and memory or other cognitive functions”. Therefore, at this time no specific mechanism could be determined for fluoride effects on learning and memory or other neurodevelopmental or cognitive outcomes.
Coherence	Coherence with previous evidence cannot be assessed based on the findings: • No specific mechanisms were directly linked to fluoride and IQ • Non-human evidence was inconclusive/inadequate
Experimental evidence	• There has been no experimental evidence generated from human studies. • The most recent systematic review of experimental evidence[xlii] found that the animal data were inadequate to evaluate the effects of fluoride on learning and memory due to reasons such as difficulty in parse out the observed learning and memory effects from the effects on motor activity or motor coordination and concerns of study quality. Additionally, one of the highest quality experimental studies [231] found no fluoride treatment related effects on learning, memory or motor activity in rats provided with up to 20 ppm concentration in drinking water • This review concluded that “the experimental animal body of evidence does not contribute to confidence in conclusions derived from human epidemiological studies with respect to effects on human IQ. Although the evidence supports an association between fluoride exposure and neurodevelopmental effects, the data are not sufficient to support the primary effect evaluated in children (i.e., IQ) nor is it sufficient to

[xlii] US NTP (2020) conducted a systematic review (including risk of bias assessment) of evidence on F induced neurodevelopmental and cognitive effects in experimental studies (non-human animals)

	support a conclusion on cognitive effects in adults especially in the absence of additional adult human data"
Analogy	No suitable analogies identified

Strength of association

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Cui 2020 [42]	Mean (±SD) IQ by urinary fluoride levels • < 1.6 mg/L: 112.16 (±11.50) • 1.6 – 2.5 mg/L: 112.05 (±12.01) • ≥ 2.5 mg/L: 110.00 (±14.92)	0.578	*Non-significant association*	Children/ adolescents
Soto-Barreras 2019 [67]	Mean (±SD) water fluoride levels (mg/L) by intellectual grade categories • Grade I: 1.48 ± 1.13 • Grade II: 1.05 ± 1.06 • Grade III: 1.04 ± 1.06 • Grade IV: 0.97 ± 1.10 • Grade V: 0.79 ± 1.17	0.645	*No association*	Children/ adolescents
	Mean (±SD) urinary fluoride levels (mg/L) by intellectual grade categories • Grade I: 0.45 ± 0.34 • Grade II: 0.54 ± 0.29 • Grade III: 0.61 ± 0.38 • Grade IV: 0.56 ± 0.33	0.559		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	• Grade V: 0.35 ± 0.19			
	Mean (±SD) exposure dose/daily intake by intellectual grade categories • Grade I: 0.03 ± 0.03 • Grade II: 0.026 ± 0.03 • Grade III: 0.027 ± 0.03 • Grade IV: 0.029 ± 0.03 • Grade V: 0.016 ± 0.02	0.389		
Bashash 2017 [85]	Change in outcome per 0.5 mg/L increase in maternal urinary fluoride levels ○ *GCI: β = -3.15 (-5.42, -0.87)* ○ *IQ: β = -2.50 (-4.12, -0.59)*	*p = 0.01* *p = 0.01*	Positive	Children/ adolescents
	Change in outcome per 0.5 mg/L increase in child urinary fluoride levels ○ *IQ – Without adjustment of maternal urinary fluoride levels: β = - 0.89 (-2.63, 0.85)* ○ *IQ – With adjustment of maternal urinary fluoride levels β = - 0.77 (-2.53, 0.99)*	*Non-significant* *Non-significant*		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Cui 2018 [72]	Change (95% CI) in IQ score per log-unit increase in urinary fluoride among all participants and by subgroups	*p = 0.236*	Positive	Children/ adolescents
	Overall (N = 323) *β = -2.47 (-4.93, - 0.01), p = 0.049* *[Bootstrapped estimate: 95%CI = -4.97, 0.03]*	*p = 0.053*		
	DRD2 SNP of CC or CT (N = 279) *β = - 1.59 (- 4.24, 1.05)* *[Bootstrapped estimate: 95%CI= -4.14, 0.95]*	*p = 0.236* *p = 0.220*		
	DRD2 SNP of TT (N = 44) *β = -12.31 (-18.69, -5.94), p=< 0.001* *[Bootstrapped estimate: 95%CI= -19.66, -4.96]* The safety threshold of urine fluoride levels in the subgroup TT: 1.73 mg/L (1.51-1.97)	*p=< 0.001* *p = 0.001*		
Kousik 2016 [90]	Correlation between exposure dose and IQ: r = -0.343	p < 0.01	Positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Mustafa 2018 [78]	Correlation between average level of fluoride in drinking water (mg/L) and average school performance score (%): Overall score: r = -0.51	p = 0.007	Possible positive	Children/ adolescents
	Correlation between average level of fluoride in drinking water (mg/L) and the prevalence of high school performance score (%): Overall score: r = -0.48	p = 0.012		
Till 2020 [53]	An increase of 0.5 mg/L in water fluoride concentration (almost equal to the difference between fluoridated and non-fluoridated regions) corresponded to reduction in performance IQ: • Formula-fed: 9.3-point (95% CI: −13.77, −4.76) • Breastfed: 6.2-point (95% CI: −10.45, −1.94). Association remained significant upon controlling for fetal fluoride exposure • Formula-fed: (b =−7.93, 95% CI: −12.84, −3.01)	Significant	Positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	• Breastfed: (b =−6.30, 95% CI: −10.92, −1.68)			
Wang 2020 [54]	Change in IQ scores per 1 mg/L increment of water fluoride • Water fluoride (continuous): b =−1.59 (−2.61, −0.57), p=0.002 Change in IQ scores per quartile increment of water fluoride compared to the reference (≤0.70 mg/L) • Water fluoride (1.00–1.90): −3.07 (−5.64, −0.49), p: 0.02	Significant	Positive	Children/ adolescents
Yu 2018 [83]	Odds (95% CI) of having excellent IQ level per 0.5 mg/L increment of fluoride in water; normal IQ is the control • Fluoride level of 0.20 – 1.40 mg/L: OR = 0.60 (0.47, 0.77) • Fluoride level of 1.40 – 3.90 mg/L: OR = 1.09 (0.88, 1.36)		Positive	Children/ adolescents

Consistency

Study	Design	Country	Population	Association	Time period
Ahmad 2022 [8]	Cross-sectional	Pakistan	Children/ adolescents	None	NR
Feng 2022 [9]	Cross-sectional	Pakistan	Children/ adolescents	Positive	2017
Goodman 2022 [11]	Cohort	Mexico	Mother/child pairs	Positive	Cohort 2A: 1997-1999 Cohort 3: 2001-2003
Ibarluzea 2022 [13]	Cohort	Spain	Mother/child pairs	None	1997-2008
Kaur 2022 [14]	Cross-sectional	India	Children/ adolescents	Positive	2011
Cui 2020 [42]	Cross-sectional	China	Children/ adolescents	Non-significant	2014 - 2018
Saeed 2022 [18]	Cross-sectional	Pakistan	Children/ adolescents	Positive	NR
Farmus 2021 [26]	Cohort	Canada	Mother/child pairs	Positive	2008-2011
Wang 2021 [37]	Cross-sectional	China	Children/ adolescents	Positive	2015
Yani 2021 [38]	Cross-sectional	Indonesia	Children/ adolescents	Positive	NR
Yu 2021 [39]	Cross-sectional	China	Children/ adolescents	Positive	2015
Zhao 2021 [40]	Cross-sectional	China	Children/ adolescents	Positive	2018
Cui Y 2020 [42]	Cross-sectional	China	Children/ adolescents	Positive	2014-2018
Till 2020 [53]	Cohort	Canada	Mother/child pairs	Positive	2008-2011
Wang 2020 [54]	Cross-sectional	China	Children/ adolescents	Positive	2015

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Soto-Barreras 2019 [67]	Cross-sectional	Mexico	Children/ adolescents	None	2017
Cui Y 2018 [72]	Cross-sectional	China	Children/ adolescents	Positive	2014-2015
Mustafa 2018 [78]	Cross-sectional	Sudan	Children/ adolescents	Possible	NR
Yu 2018 [83]	Cross-sectional	China	Children/ adolescents	Positive	2015
Bashash 2017 [85]	Cohort	Mexico	Mother/child pairs	Positive	1997-1999 2001-2003
Heck 2016 [89]	Cross-sectional	United States	Adults, children/ adolescents	None	NR
Kousik 2016 [90]	Cross-sectional	India	Children/ adolescents	Positive	NR

Temporality

Study	Design	Outcome, time of assessment
Bashash 2017 [85]	Cohort	• GCI scores at the age of 4 • Full-Scale IQ scores at the age of 6–12
Till 2020 [53]	Cohort	• IQ scores at the age of 3-4
Kousik 2016 [90]	Cross-sectional	N/A
Mustafa 2018 [78]	Cross-sectional	N/A
Wang 2020 [54]	Cross-sectional	N/A
Cui 2018 [72]	Cross-sectional	N/A
Yu 2018 [83]	Cross-sectional	N/A

Biological gradient (exposure-response)

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Bashash 2017 [85]	Change in outcome per 0.5 mg/L increase in maternal urinary fluoride levels		Positive	Mother/child pairs
	○ *GCI: β = -3.15 (-5.42, -0.87)*	*p = 0.01*		
	○ *IQ: β = -2.50 (-4.12, -0.59)*	*p = 0.01*		
	Change in outcome per 0.5 mg/L increase in child urinary fluoride levels			
	○ *IQ – Without adjustment of maternal urinary fluoride levels:* *β = - 0.89 (-2.63, 0.85)*	*Non-significant*		
	○ *IQ – With adjustment of maternal urinary fluoride levels* *β = - 0.77 (-2.53, 0.99)*	*Non-significant*		
Cui 2018 [72]	Change (95% CI) in IQ score per log-unit increase in urinary fluoride among all participants and by subgroups		Positive	Children/ adolescents
	Overall (N = 323)			

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	β = -2.47 (-4.93, - 0.01), p = 0.049	*p = 0.236*		
	[Bootstrapped estimate: 95%CI = -4.97, 0.03]	*p = 0.053*		
	DRD2 SNP of CC or CT (N = 279)			
	β = - 1.59 (- 4.24, 1.05)	*p = 0.236*		
	[Bootstrapped estimate: 95%CI= -4.14, 0.95]	*p = 0.220*		
	DRD2 SNP of TT (N = 44)			
	β = -12.31 (-18.69, -5.94), p=< 0.001	*p=< 0.001*		
	[Bootstrapped estimate: 95%CI= -19.66, -4.96]	*p = 0.001*		
	The safety threshold of urine fluoride levels in the subgroup TT: 1.73 mg/L (1.51-1.97)			
Kousik 2016 [90]	Correlation between exposure dose and IQ: r = -0.343	p = < 0.01	Positive	Children/ adolescents
Mustafa 2018 [78]	Correlation between average level of fluoride in drinking water (mg/L) and average school performance score (%):	p = 0.007	Possible positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	Overall score: r = -0.51			
	Correlation between average level of fluoride in drinking water (mg/L) and the prevalence of high school performance score (%): Overall score: r = -0.48	p = 0.012		
Till 2020 [53]	An increase of 0.5 mg/L in water fluoride concentration (almost equal to the difference between fluoridated and non-fluoridated regions) corresponded to reduction in performance IQ: • Formula-fed: 9.3-point (95% CI: −13.77, −4.76) • Breastfed: 6.2-point (95% CI: −10.45, −1.94). Association remained significant upon controlling for fetal fluoride exposure • Formula-fed: (β =−7.93, 95% CI: −12.84, −3.01) • Breastfed: (β =−6.30, 95% CI: −10.92, −1.68)	Significant	Positive	Mother/child pairs
Wang 2020 [54]	Fluoride exposure was inversely related to IQ scores	P=0.002	Positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	• Water fluoride: β =−1.59 (95% CI: −2.61, −0.57)			
Yu 2018 [83]	Odds (95% CI) of having excellent IQ level per 0.5 mg/L increment of fluoride in water; normal IQ is the control • Fluoride level of 0.20 – 1.40 mg/L: OR = 0.60 (0.47, 0.77) • Fluoride level of 1.40 – 3.90 mg/L: OR = 1.09 (0.88, 1.36)		Positive	Children/ adolescents

7.2. Thyroid dysfunction

Criterion	**Summary of Evidence**
Strength of association	• Six studies of high/acceptable quality reported results demonstrating a positive/possible association between thyroid dysfunction and water [54, 74, 76, 81] or urinary fluoride [25]. • One study [74] reported a higher percent thyroid hormone level derangement in fluorosis-endemic areas (67.5%) compared to non-endemic areas (54%), and a significant increase in mean TSH (endemic: 3.849 µlU/m; non-endemic: 2.588 µlU/m, p = 0.02). Non-significant derangements were reported for mean free T3, and free T4 levels among participants from a fluorosis-endemic area compared to a fluorosis non-endemic area. • Another study [81] reported on levels of free T3, free T4, and TSH by villages belonging to one of four groups based on the fluoride levels in drinking water. These levels range from <1 ppm (group 1), 1-1.9 ppm (group 2), 2-2.9 ppm (group 3) and >4 ppm (group 4). Derangement of TSH (range of normal values: 0.5–2.5 µIU/mL) has been shown in all groups. However, only group 1 (TSH: 0.4-2.99 µIU/mL) and group 2 (TSH: 0.29-3.76 µIU/mL) were relevant to North American water fluoride levels. • The third study [54] reported a change in thyroid hormone levels per 1 mg/L increment of water fluoride (continuous) or compared to a reference quartile. Only hormones with significant results are listed below. **TT4 (µg/dL)** ▪ Continuous: β= −0.083 (−0.181, 0.015), p-value= 0.097 ▪ Quartiles: β= (95% CI), p-value ○ Quartile 1 (≤0.70): reference

- Quartile 2 (0.70–1.00): β= −0.376(−0.686, −0.066), p-value= 0.017
- Quartile 3 (1.00–1.90): β= −0.442(−0.687, −0.198), p-value= < 0.01
- Quartile 4 (> 1.90): β= −0.271(−0.522, −0.020), p-value= 0.034
- P-trend: 0.036

FT4 (ng/dL)

- Continuous: β= −0.010 (−0.021, 0.000), p-value= 0.054
- Quartiles: β= (95% CI), p-value
  - Quartile 1 (≤0.70): reference
  - Quartile 2 (0.70–1.00): β= −0.030 (−0.063, 0.003), p-value= 0.072
  - Quartile 3 (1.00–1.90): β= −0.027 (−0.053, −0.001), p-value= 0.042
  - Quartile 4 (> 1.90): β= −0.037 (−0.063, −0.010), p-value= 0.007
  - P-trend: 0.009

TSH (μIU/mL)

- Continuous: β= 0.127 (0.014, 0.241), p-value= 0.028
- Quartiles: β= (95% CI), p-value
  - Quartile 1 (≤0.70): reference
  - Quartile 2 (0.70–1.00): β= −0.154 (−0.517, 0.209), p-value= 0.404
  - Quartile 3 (1.00–1.90): β= 0.236 (−0.005, 0.522), p-value= 0.106
  - Quartile 4 (> 1.90): β= 0.306(0.012, 0.600), p-value= 0.041
  - P-trend: 0.019

	• A fourth study [76] reported that every 1mg/L increment of urinary fluoride (in iodine-deficient adults) was associated with a 0.35 mIU/L increase in TSH [95% CI: 0.06, 0.64, p-value: 0.01, one-tailed].
Consistency	• Four studies [54, 74, 76, 81] found a positive association between thyroid dysfunction and higher exposure to water fluoride. • Two additional studies reported a possible [76], or a non-significant association [42] between urinary fluoride levels and thyroid dysfunction. • Within studies showing a positive/possible association, the directionality of association did not differ by study design (all studies were cross-sectional), geographic location (two in India and one in each of Canada and China), studied population (three studies in children/adolescents and one included all ages), or sampling timeframe. • Two additional studies of acceptable quality identified by CADTH 2019 [396] and the current review [66] reported no association between fluoride and thyroid function.
Specificity	Fluoride appears to play a role in the induction of a range of adverse health outcomes, and dysregulating thyroid hormone levels can be caused by a number of risk factors including exposure to toxic factors other than fluoride.
Temporality	All of the four studies that suggest a positive/possibly positive association were of cross-sectional study designs, whereby an inference of causality cannot be inferred.
Biological gradient (exposure-response)	• Six studies reported results supporting a positive/possible association between thyroid dysfunction in association with either water fluoride levels as categories [74, 81], or on a continuous scale [54, 76], or using urinary fluoride levels [25, 42].

	• One study reported on four groups of exposure, and identified a consistent increase in mean levels of free T3, free T4, and TSH per increase in concentrations of fluoride in water [81]. • Another study reported that each 1mg/L increment of water fluoride is associated with an increase in TSH, FT3 and TT3, and a decrease in FT4 and TT4. However, the effect estimate for TSH was only statistically significant before correcting for multiple testing [54]. • A third study [74] reported a higher thyroid hormone level derangement in fluorosis-endemic areas compared to non-endemic areas. This derangement was significant for TSH and non-significant for FT3 and FT4 levels. • The study by Malin et al. [76] reported that each 1mg/L increment of urinary fluoride (in iodine-deficient adults) is associated with a 0.35 mIU/L increase in TSH.
Biological plausibility	• As halogens of lower atomic weight are capable of displacing halogens of higher atomic weight, fluoride (fluorine) can displace iodine from the body. Such displacement thus interferes with iodine uptake by the thyroid gland, leading to its dysfunction and increased secretion of the pituitary TSH hormone to stimulate the thyroid to produce more thyroid hormones [76, 81]. • The effect of fluoride on thyroid function may depend on nutritional status and iodine deficiency. In the North American context, iodine deficiency is unlikely given that the intake exceeds 1mg/day due to the use of iodized salt [1]. However, the evidence also suggests that the effect of fluoride on the thyroid gland can occur independently of iodine [54]. • Interference of fluoride with Na/K-ATPase and iodothyronine deiodinase: two enzymes that are required for proper thyroid functioning [76]. • Fluoride may inhibit the prolactin hormone, which promotes thyroidal iodine uptake, lowers T4 secretion and inhibits stimulatory effects of exogenous TSH [76].

	• Fluoride is a structural analog of thyroid stimulating hormone (TSH) and able to bind to TSH receptors leading to change in TSH levels and changes in secretion of thyroid hormones (by altering the regulation of hypothalamus-pituitary-thyroid axis) • The other plausible mechanism by which excess fluoride may affect thyroid structure and function is to induce endoplasmic reticulum stress pathways and subsequent apoptosis leading to cell death and changes in thyroid follicle morphology
Coherence	Coherence with previous evidence cannot be assessed based on the findings: • No specific mechanisms were directly linked to fluoride and thyroid dysfunction • Animal evidence was inconclusive
Experimental evidence	• There has been no experimental evidence generated from human studies. • Two experimental studies [210], [231] were identified, which evaluated fluoride effects on thyroid function (changes in thyroid hormone levels) at test concentrations required to achieve comparable blood fluoride levels in humans exposed to drinking water in Canada and are of lower risk of bias (more details are provided in the table containing results from selected animal studies) • Out of two studies (both were rat chronic studies), one study didn't find an association between increase in fluoride concentration and change in thyroid hormone levels; the other study reported inconsistent evidence (across two time points) on small but significant change in TSH and serum T4 levels.
Analogy	No suitable analogies identified

Strength of association

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
Du 2021 [25]	**Tvol (cm3)**		*Positive association*	Children/ adolescents
	• All: β (95% CI): 0.22 (0.14, 0.31), p-value:	< 0.001		
	• Boys: β (95% CI): 0.34 (0.20, 0.48)	< 0.001		
	• Girls: β (95% CI): 0.14 (0.03, 0.24)	0.011		
	• Interaction: β (95% CI): − 0.15 (− 0.30, − 0.01)	0.038		
	TT4 (nmol/l)			
	• All: β (95% CI): 1.44 (− 1.28, 4.16)	0.297		
	• Boys: β (95% CI): 2.13 (− 2.89, 7.14)	0.404		
	• Girls: β (95% CI): 0.89 (− 2.27, 4.04)	0.580		
	• Interaction: β (95% CI): − 1.46 (− 6.17, 3.24)	0.542		
	TT3 (nmol/l)			
	• All: β (95% CI): − 0.05 (− 0.10, 0.01), p-value:	0.087		
	• Boys: β (95% CI): − 0.08 (− 0.17, 0.01)	0.072		

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	• Girls: β (95% CI): − 0.03 (− 0.10, 0.04)	0.381		
	• Interaction: β (95% CI): 0.01 (− 0.08, 0.10)	0.795		
Cui 2020 [42]	Median (q1-q3) TSH in uIU/mL by urinary fluoride levels • < 1.6 mg/L: 2.81 (2.21 – 3.81) • 1.6 – 2.5 mg/L: 2.82 (2.01 – 3.82) • ≥ 2.5 mg/L: 3.29 (2.30 – 4.48)	0.287	Non-significant association	Children/ adolescents
Kumar 2018 [74]	Thyroid hormone (Mean) levels by study group *(A: fluorosis endemic area, B: fluorosis non-endemic area)* • Free T3 (pg/ml): A: 3.125; B: 2.698	p = 0.26	Positive	Children/ adolescents
	• Free T4 (ng/dL): A: 1.282; B: 1.193	p = 0.41		
	• TSH (µlU/m): A: 3.849; B: 2.588	p = 0.02		
	• Percent (%) of thyroid hormone level derangement: A: 67.5; B: 54			
Rathore 2018 [81]	• Exposure groups: Gp 1: <1ppm Gp 2: 1-1.9 ppm	P value: NR	Positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	Gp 3: 2-3.9 ppm Gp 4: ≥ 4ppm • Free T3: mean, ±SD, [range] (pg/mL) *Gp 1: 2.66 pg/mL ±0.46, [2.11 – 3.89]* *Gp 2: 2.73 pg/mL ±0.36, [2.13 – 3.56]* *Gp 3: 2.84 pg/mL ±0.46, [2.02 – 4.26]* *Gp 4: 3.06 pg/mL ±0.78, [1.91 – 4.42]* • Free T4: mean ±SD, [range] (ng/dL) *Gp 1: 0.98 ng/dL ±0.21, [0.79 – 1.79]* *Gp 2: 1.02 ng/dL ±0.26, [0.78 – 1.89]* *Gp 3: 1.11 ng/dL ±0.28, [0.76 – 1.98]* *Gp 4: 1.22 ng/dL ± 0.33, [0.75 – 1.89]* • TSH: Mean ± SD, [range] (µIU/mL) *Gp 1: 1.33 µIU/mL ±0.78, [0.4 – 2.99]* *Gp 2: 1.64 µIU/mL ±0.88), [0.29 – 3.76]* *Gp 3: 1.86 µIU/mL ±0.77, [0.76 – 3.74]* *Gp 4: 1.91 uIU/mL ±1.10, [0.75 – 4.99]*			

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
Wang 2020 [54]	Every 1 mg/L increment of water fluoride was associated with • *0.006 ng/mL increase in TT3* • *0.013 pg/mL increase in FT3* • *0.083 ng/mL decrease in TT4* • *0.01 ng/mL decrease in FT4* • *0.13 µIU/mL increase in TSH*	P=0.028 (significant only before correction for multiple testing)	Positive	Children/ adolescents
	Every 1 mg/L increment of urinary fluoride was associated with • *0.007 ng/mL increase in TT3* • *0.02 pg/mL increase in FT3* • *0.09 ng/mL decrease in TT4* • *0.009 ng/mL decrease in FT4* • *0.11 µIU/mL increase in TSH*	0.013 (Remained significant after corrections for multiple testing)		
Malin 2018 [76]	Every 1mg/L increment of urinary fluoride (in iodine-deficient adults) was associated with a 0.35 mIU/L increase in TSH [95% CI: 0.06,	p = 0.01 (one-tailed)	Possible positive	Children/ adolescents and adults

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	0.64].			

Consistency

Study	Design	Country	Population	Time period
Du 2021 [25]	Cross-sectional	China	Children/ adolescents	2017
Cui 2020 [42]	Cross-sectional	China	Children/ adolescents	2014 - 2018
Kumar 2018 [74]	Cross-sectional	India	Children/ adolescents	NR
Rathore 2018 [81]	Cross-sectional	India	Children/ adolescents	NR
Wang 2020 [54]	Cross-sectional	China	Children/ adolescents	2015
Malin 2018 [76]	Cross-sectional	Canada	Children/ adolescents and adults	2012 – 2013

Biological gradient (exposure-response)

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
Kumar 2018 [74]	Thyroid hormone (Mean) levels by study group (A: fluorosis endemic area, B: fluorosis non-endemic area) • Free T3 (pg/ml): A: 3.125; B: 2.698	p = 0.26		
	• Free T4 (ng/dL): A: 1.282; B: 1.193	p = 0.41		
	• TSH (µlU/m): A: 3.849; B: 2.588	p = 0.02		
	• Percent of thyroid hormone level derangement: A: 67.5; B: 54			
Rathore 2018 [81]	• Exposure groups: Gp 1: <1ppm Gp 2: 1-1.9 ppm Gp 3: 2-3.9 ppm Gp 4: ≥ 4ppm • Free T3: mean, ±SD, [range] (pg/mL) *Gp 1: 2.66 pg/mL ±0.46, [2.11 – 3.89]* *Gp 2: 2.73 pg/mL ±0.36, [2.13 – 3.56]*	P value: NR	Positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	Gp 3: 2.84 pg/mL ±0.46, [2.02 – 4.26] *Gp 4: 3.06 pg/mL ±0.78, [1.91 – 4.42]* • Free T4: mean ±SD, [range] (ng/dL) *Gp 1: 0.98 ng/dL ±0.21, [0.79 – 1.79]* *Gp 2: 1.02 ng/dL ±0.26, [0.78 – 1.89]* *Gp 3: 1.11 ng/dL ±0.28, [0.76 – 1.98]* *Gp 4: 1.22 ng/dL ± 0.33, [0.75 – 1.89]* • TSH: Mean ± SD, [range] (µIU/mL) *Gp 1: 1.33 µIU/mL ±0.78, [0.4 – 2.99]* *Gp 2: 1.64 µIU/mL ±0.88), [0.29 – 3.76]* *Gp 3: 1.86 µIU/mL ±0.77, [0.76 – 3.74]* *Gp 4: 1.91 uIU/mL ±1.10, [0.75 – 4.99]*			
Wang 2020 [54]	Every 1 mg/L increment of water fluoride was associated with • *0.006 ng/mL increase in TT3* • *0.013 pg/mL increase in FT3*	P=0.028 (significant only before	Positive	Children/ adolescents

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Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	• *0.083 ng/mL decrease in TT4* • *0.01 ng/mL decrease in FT4* • *0.13 µIU/mL increase in TSH*	correction for multiple testing)		
	Every 1 mg/L increment of urinary fluoride was associated with • *0.007 ng/mL increase in TT3* • *0.02 pg/mL increase in FT3* • *0.09 ng/mL decrease in TT4* • *0.009 ng/mL decrease in FT4* • *0.11 µIU/mL increase in TSH*	0.013 (Remained significant after corrections for multiple testing)		
Malin 2018 [76]	Change (95%CI) in serum TSH (µIU/L) per unit increase in UFsg (mg/L) No iodine deficiency: ß = -0.02 (-0.19, 0.15)	p = 0.43	Possible positive	Children/ adolescents and adults
	Iodine deficiency: ß = 0.36 (-0.03, 0.75)	p = 0.03		

Experimental evidence

Selected animal studies (tier-1; medium to high quality) investigating thyroid dysfunction

Animal model	F in DW[xliii] (mg/L)	Significantly altered outcomes	D-R trend
Rat (chronic) (943)	0, 5, 10, 20	Serum T4, FT4 and TSH levels (no change in serum T3, FT3)	Inconsistent change across time points and only occurred at higher doses
Rat (chronic)[xliv]	0, 10, 20	None (serum T3, T4 and TSH levels were assessed)	None

[xliii] "[t]he fluoride concentration in drinking water for rats must be about 4–5 times greater in order to achieve serum fluoride levels comparable to those in humans (Angmar-Mansson and Whitford, 1984)" (as cited in Cardenas-Gonzalez et al., 2013) (NRC, 2006; McPherson et al, 2018)

[xliv] McPherson CA, Zhang G, Gilliam R, Brar SS, Wilson R, Brix A, Picut C, Harry GJ. 2018. An evaluation of neurotoxicity following fluoride exposure from gestational through adult ages in Long-Evans hooded rats. Neurotoxicol Res: 1-18.

7.3. Kidney dysfunction

Criterion	**Summary of Evidence**

Strength of association	• Four studies [49, 57, 62, 73] of high/acceptable quality reported results demonstrating a possible association between kidney dysfunction and fluoride exposure.
	  • One study [73] reported a significantly positive association for each unit increase in water fluoride (mg/L) with ALB (β=1.20 µg/mL), Cys-C (β=0.03 mg/mL), OPN (β=0.10 mg/mL), TFF-3 (β=2.88 ng/mL). Change in CLU, KIM-1, and eGFR was non-significant.
	  • Another study reported an inverse association per each 1mg/L increase in water fluoride with BUN concentration (β=−0.93 mg/dL, [−1.44, −0.42], p=0.007), whereas change in eGFR and ACR were non-significant. Additionally, a positive association was observed with SUA (non-significant) [62].
	  • A third study [57] reported a significant increase in serum fluoride of 1.43 (0.47–9.58) in CKDu patients compared to 1.07 (0.51–1.92) in controls. Similarly, a significant increase was reported for urinary fluoride as 1.53 ([0.45–6.92) in CKDu patients compared to 1.26 (0.36–3.80) in controls.
	  • The fourth study [49] also reported that CKDu patients showed significantly higher serum fluoride concentrations than the healthy controls (p-value: <0.05).

Consistency	• Four studies [49, 57, 62, 73] suggested a possible association between kidney dysfunction and fluoride exposure.

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	• Within studies showing a possible association, 3 studies were cross-sectional [49, 62, 73] and 1 was a case-control [57], geographic location included Mexico, Sri Lanka, and United States, and the studied population involved children/adolescents [62, 73] and adults [49, 57]. • The directionality of the association (positive vs. inverse association) varied depending on the indicator of kidney dysfunction assessed. • Two additional studies reported inconclusive [58] or no association [87] between water fluoride and kidney dysfunction.
Specificity	Fluoride appears to play a role in the induction of a range of adverse health outcomes, and kidney dysfunction can be caused by a number of risk factors including exposure to toxic factors other than fluoride.
Temporality	Of the 4 studies that suggested a possible association, 3 were of cross-sectional design [49, 62, 73], whereby an inference of causality should not be inferred.
Biological gradient (exposure-response)	Of the two studies [62, 73] that reported results supporting a possible association between water fluoride levels and kidney dysfunction, both examined the exposure on a continuous scale. • One study reported a positive association for each unit increase in water fluoride (mg/L) with ALB (albumin), Cys-C (cystatin-C), OPN (osteopontin), TFF-3 (trefoil factor 3, significant), CLU (clusterin), KIM-1 (kidney injury molecule 1), and eGFR (estimated glomerular filtration rate, non-significant) [73]. • The other study reported an inverse association for each 1mg/L increase in water fluoride with BUN (blood urea nitrogen, significant), eGFR, and ACR (urinary albumin to creatinine ratio, non-

	significant). Additionally, a positive association was observed with SUA (serum uric acid, non-significant) [62].
Biological plausibility	• Histopathological changes in the kidney due to high fluoride exposure [57]. • Increased apoptosis and tubular epithelial damage, including necrosis, have also been observed among children with high fluoride exposures [62]. • Studies with adult rats have shown that chronic low-level fluoride exposure can lead to glomerular hypercellularity and mesangial cell proliferation, reduced kidney enzyme activity, interstitial nephritis, and renal tubule hypertrophy and hyperplasia [62]. • In experimental studies, exposure to fluoride has been associated with enzymatic inhibition, mitochondrial dysfunction (by the sirtuin 3 (SIRT3) pathway), oxidative stress generation and apoptosis induction (via activation of Bax expression and Bcl-2), especially in the S3 segment of the proximal tubules, which is considered the section most susceptible to fluoride toxicity [73] • In animal models, these kidney toxicants have been shown to target predominantly the proximal tubule causing reactive oxygen species generation followed by endoplasmic reticulum stress and mitochondrial damage, culminating in cellular necrosis/apoptosis [87]. • In humans, chronic exposure to heavy metals and fluoride has been associated with kidney disease. However, most of these studies have been conducted in adults that are occupationally exposed and therefore, the effects of environmental exposure in children largely remains uninvestigated [87]. • Primary route of elimination is fluoride through kidneys and large number of experimental studies provide evidence that tubular area of kidneys is the most vulnerable to excess amounts of fluoride [135, 397].

	• One of the plausible mechanisms of fluoride induced kidney damage particularly in renal tubules is by increasing lipid peroxidation and decreasing activities of antioxidant enzymes (oxidative stress) at cellular level or by activating apoptotic pathways leading to cell death and renal injury.
Coherence	Coherence with previous evidence cannot be assessed based on the findings: • No specific mechanisms were directly linked to fluoride and kidney dysfunction • Animal evidence was inconclusive/inadequate
Experimental evidence	• There has been no experimental evidence generated from human studies. • Six experimental studies [135, 139, 172, 197, 255, 305] were identified that evaluated fluoride effects on kidney function at test concentrations required to achieve comparable blood fluoride levels in humans exposed to drinking water in Canada and are of lower risk of bias • These studies investigated the impact of fluoride exposure in rodents (mice or rats) at different exposure durations (chronic or sub-chronic) given a range of drinking water fluoride concentrations (ranged from 0.05 – 150 mg/L); specific outcomes measured include kidney dysfunction markers such as blood urea nitrogen (BUN) or creatinine (CRE) levels or histological analysis • Three out of six studies found some histopathological changes in kidneys (such as proximal tubule injury) but none reported any significant changes in kidney dysfunction markers such as BUN or CRE at or above test concentrations relevant to humans (except one study found slight but significant increase in CRE levels after long term exposure at 20 ppm fluoride concentrations)
Analogy	No suitable analogies identified

Strength of association

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
Nanayakkara 2020 [49]	Mean serum fluoride level (±SD) by CKDu stage • Stage 0: 35.5 µg/L (±16.3)	p<0.05 * compared to controls	Possible	Adult non-dialysis CKDu cases
	• Stage 1: 38.1 µg/L (±18.1)			
	• Stage 2: 53.9 µg/L (±34.2) *			
	• Stage 3: 82.8 µg/L (±41.9) *			
	• Stage 4: 123.4 µg/L (±59.9) *			
	• Stage 5: 123.9 µg/L (±52.6) *			
Fernando 2019 [93]	• Serum fluoride: Mean ±SD [range] mg/L *CKDu patients: 1.43 ±1.2 [0.47 – 9.58]* *Controls: 1.07 ±0.3 mg/L [0.51 – 1.92]* *p = 0.000 (showed a significant difference based on CKDu stage but not with sex or age)*	p = 0.000	Possible	Adult non-dialysis CKDu cases
	• Urinary fluoride: Mean ±SD [range] mg/L	p = 0.004		

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	CKDu patients: 1.53 ±0.8 [0.45 – 6.92] *Controls: 1.26 ±0.63 [0.36 – 3.80]*			
Malin 2019 [62]	1 mg/L increase in water fluoride was associated with: • 0.93 mg/dL lower blood urea nitrogen concentration (95% CI: −1.44, −0.42).	p=0.007	Possible	Children/ adolescents
	• eGFR: -1.03 mL/min/m2 (95% CI: -2.93, 0.87) *Water fluoride was log2 transformed in this model.*	p > 0.99		
	• SUA: 0.05 mg/dL (95% CI: -0.07, 0.18)	p > 0.99		
	• ACR: -0.01 mg/g (95% CI: -0.07, 0.06) *Water fluoride and outcome variables were log2 transformed.*	p > 0.99		
	1 µmol/L increase in plasma fluoride was associated with: • 10.36 mL/min/1.73m2 lower estimated glomerular filtration rate (95% CI: −17.50, −3.22)	p=0.05		
	• 0.29 mg/dL higher serum uric acid concentration (95% CI: 0.09, 0.50)	p=0.05		

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	• 1.29 mg/dL lower blood urea nitrogen concentration (95%CI: −1.87, −0.70)	p < 0.001		
Jimenez-Cordova 2018 [73]	Change in outcome (p-value) per unit increase of fluoride in water (mg/L) and urine (µg/mL)		Possible	Adults
	• ALB (µg/mL)			
	Water: β= 1.20	p= <0.001		
	Urine: β= 0.56	p= <0.001		
	• Cys-C (mg/mL)			
	Water: β= 0.03	p= 0.005		
	Urine: β= 0.022	p= 0.001		
	• OPN (mg/mL)			
	Water: β= 0.10	p= 0.028		
	Urine: β= 0.038	*p= 0.041*		
	• CLU (µg/mL)			
	Water: β= 0.09	p= 0.118		
	Urine: β= 0.07	p= 0.100		

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	• KIM-1 (ng/mL)			
	Water: b= 0.045	p= 0.162		
	Urine: b= 0.048	p= 0.008		
	• TFF-3 (ng/mL)			
	Water: β= 2.88	p= 0.010		
	Urine: β= 1.14	p= 0.115		
	• eGFR (mL/min/1.73 m2)			
	Water: β= 0.19	p= 0.675		
	Urine: β= 0.49	p= 0.030		

Consistency

Study	Design	Country	Association	Population	Time period
Nanayakkara 2020 [49]	Cross-sectional	Sri Lanka	Possible	Adult CKDu cases	NR
Fernando 2019 [93]	Case-control	Sri Lanka	Possible	Adult non-dialysis CKDu cases	NR
Jimenez-Cordova 2019 [58]	Cross-sectional	Mexico	Inconclusive	Children/ adolescents	2015
Malin 2019 [62]	Cross-sectional	United States	Possible	Children/ adolescents	2013–2016
Jimenez-Cordova 2018 [73]	Cross-sectional	Mexico	Possible	Adults	2013
Cardenas-Gonzalez 2016 [87]	Cross-sectional	Mexico	None	Children/ adolescents	2014

Biological gradient (exposure-response)

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
Nanayakkara 2020 [49]	Mean serum fluoride level (±SD) by CKDu stage • Stage 0: 35.5 µg/L (±16.3) • Stage 1: 38.1 µg/L (±18.1) • Stage 2: 53.9 µg/L (±34.2) * • Stage 3: 82.8 µg/L (±41.9) * • Stage 4: 123.4 µg/L (±59.9) * • Stage 5: 123.9 µg/L (±52.6) *	p<0.05* compared to controls	Possible	Adult non-dialysis CKDu cases
Fernando 2019 [93]	• Serum fluoride: Mean ±SD [range] mg/L *CKDu patients: 1.43 ±1.2 [0.47 – 9.58]* *Controls: 1.07 ±0.3 mg/L [0.51 – 1.92]* *p = 0.000 (showed a significant difference based on CKDu stage but not with sex or age)*	p = 0.000	Possible	Adult non-dialysis CKDu cases
	• Urinary fluoride: Mean ±SD [range] mg/L *CKDu patients: 1.53 ±0.8 [0.45 – 6.92]* *Controls: 1.26 ±0.63 [0.36 – 3.80]*	p = 0.004		

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
Malin 2019 [62]	1 mg/L increase in water fluoride was associated with: • 0.93 mg/dL lower blood urea nitrogen concentration (95% CI: −1.44, −0.42).	p=0.007	Possible	Children/ adolescents
	• eGFR: -1.03 mL/min/m2 (95% CI: -2.93, 0.87) *Water fluoride was log2 transformed in this model.*	p > 0.99		
	• SUA: 0.05 mg/dL (95% CI: -0.07, 0.18)	p > 0.99		
	• ACR: -0.01 mg/g (95% CI: -0.07, 0.06) *Water fluoride and outcome variables were log2 transformed.*	p > 0.99		
	1 µmol/L increase in plasma fluoride was associated with: • 10.36 mL/min/1.73m2 lower estimated glomerular filtration rate (95% CI: −17.50, −3.22)	p=0.05		
	• 0.29 mg/dL higher serum uric acid concentration (95% CI: 0.09, 0.50)	p=0.05		
	• 1.29 mg/dL lower blood urea nitrogen concentration (95%CI: −1.87, −0.70)	p < 0.001		
	Change in outcome (p-value) per unit increase of fluoride in water (mg/L) and urine (µg/mL)		Possible	Adults

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
Jimenez-Cordova 2018 [73]	• ALB (µg/mL)			
	Water: β= 1.20	p= <0.001		
	Urine: β= 0.56	p= <0.001		
	• Cys-C (mg/mL)			
	Water: β= 0.03	p= 0.005		
	Urine: β= 0.022	p= 0.001		
	• OPN (mg/mL)			
	Water: β= 0.10	p= 0.028		
	Urine: β= 0.038	*p= 0.041*		
	• CLU (µg/mL)			
	Water: β= 0.09	p= 0.118		
	Urine: β= 0.07	p= 0.100		
	• KIM-1 (ng/mL)			
	Water: b= 0.045	p= 0.162		
	Urine: b= 0.048	p= 0.008		

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Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	• TFF-3 (ng/mL)			
	Water: β= 2.88	p= 0.010		
	Urine: β= 1.14	p= 0.115		
	• eGFR (mL/min/1.73 m2)			
	Water: β= 0.19	p= 0.675		
	Urine: β= 0.49	p= 0.030		

Experimental evidence

Selected animal studies (tier-1; medium to high quality) investigating kidney effects

Animal model	F in DW (mg/L)	Significantly altered outcomes	D-R trend
Rat (subchronic) (219)	0, 15, 50	Histology (proximal tubule injury)	Altered at all doses tested
Rat (subchronic) (820)	0, 2.3, 23	Histology	Altered at highest dose tested
Rat (subchronic) (1260)	0, 0.5, 5, 20	Kidney function (CRE levels)	Altered at highest dose tested
Mice (subchronic) (252)	0, 6.8, 68	Histology	Altered at all doses tested
Mice (chronic) (1751)	0, 0.05, 1.5, 10	None (histology and kidney function[xlv] were assessed)	None
Mice (subchronic) (631)	0, 150,	None (kidney function was assessed)	None
Rat (subchronic) (1215)	0, 15	Histology	Single dose (tier-2 study)

[xlv] Blood urea nitrogen and creatinine levels

7.4. Sex hormone disruptions

Criterion	**Summary of Evidence**
Strength of association	• One human study [41] of high quality reported inverse association of fluoride in plasma and water with sex steroid hormones of total testosterone, where a possible biological gradient could be identified among all study groups except for male children. Similar disruptions of estradiol and sex hormone binding globulin (SHBG) could not be observed in U.S. children and adolescents. • Another human study [55] reported chronic fluoride exposure from drinking water is associated with significant differences of serum SHBG concentration among local male farmers in the high-exposure gp. (30.07 ± 28.32), compared to the low-exposure gp. (35.90 ± 28.58). The effect of fluoride exposure on androgen binding protein (ABP) levels was non-significant, and varied depending on estrogen receptor α gene (ESRα) gene polymorphisms. • All 11 experimental animal studies [132, 137, 138, 205, 206, 285, 286, 300, 307, 311, 336] identified in this review reported statistically significant changes in one or more outcomes related to male reproductive system dysfunction (male infertility) such as change in sperm quality or testosterone levels or histology of testis • These changes are observed at test concentrations relevant to humans i.e., concentrations required to achieve comparable serum fluoride levels in humans exposed to North American CWF levels. • These studies [132, 137, 138, 205, 206, 285, 286, 300, 307, 311, 336] included multiples species (rats and mice), dose ranges that relevant to current CWF levels, exposure pattern (i.e.,

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	continuous exposure through drinking water) and sufficient group size (i.e., 10 or more animals per treatment group).
Consistency	• The two identified human studies [41, 55] reported significant inverse associations with serum levels of different sex hormones in male and female adults, children and adolescents. • Drinking water fluoride studies in mice and rats over a range of study durations (chronic and sub-chronic) and doses (5 to >20 ppm) that are relevant to current drinking water levels in Canada demonstrate a consistent association on the male reproductive outcomes such as sperm quality, histology of testis and testosterone levels (see experimental evidence table for male fertility in section 5 of the current supplementary material).
Specificity	Fluoride appears to play a role in the induction of a range of adverse health outcomes, and dysregulating male reproductive system/functions can be caused by a number of risk factors including exposure to toxic factors other than fluoride.
Temporality	• The 2 human studies [41, 55] are were cross-sectional design, and an inference of causality cannot be inferred. • In all experimental animal studies, the exposure (i.e., fluoride treatment) preceded the observation of outcomes (i.e., change in male reproductive outcomes)
Biological gradient (exposure-response)	• One human study [41] of high quality reported inverse association of fluoride in plasma and water with sex steroid hormones of total testosterone, where a possible biological gradient could be identified among all study groups except for

	male children. Similar disruptions of estradiol and sex hormone binding globulin (SHBG) could not be observed in U.S. children and adolescents. • A second study by An and colleagues [55] did not provide enough comparison groups to allow for a proper assessment of a biological gradient (high exposure vs. low exposure only). • All the included experimental animal studies reported significant changes in sperm quality with changes in fluoride levels in DW • Four studies found a linear dose response relationship between fluoride concentration in DW and one or more outcomes related to sperm quality (e.g., reduction in sperm motility, count or hyperactivity or increase in sperm abnormalities)
Biological plausibility	• Animal experiments reported chronic fluoride exposure to damage Sertoli cells in, whether such damage can further alter serum ABP concentrations remains uncertain [55]. • In addition to ABP regulation by SHBG, ABP regulation in vivo has been reported to be regulated by androgen and FSH [55]. • Mounting evidence has indicated that both gene-gene and gene-environment interactions play important roles in regulating hormone levels. Males who carried different ESRα genotypes with the same fluoride exposure group had different serum ABP concentrations, suggesting that genetic polymorphisms also significantly affect serum ABP levels [55].

	• One of the plausible mechanisms proposed for fluoride induced male reproductive toxicity is reducing gene/protein expression of NGF and other genes in MAPK pathways; nerve growth factor (NGF) plays a critical role in male reproductive system such as in sperm motility, inducing proliferation and differentiation of stem Leydig cells and production of testosterone [330]. • Another proposed mechanism is by induction of reactive oxygen species mediated endoplasmic reticulum (ER) stress pathway followed by apoptosis of Sertoli cells which play an important role in spermatogenesis [398]. Several studies linked toxicant induced ER stress pathways to impairment of male reproductive function such as changes in spermatogenesis, sperm function/ hyperactivation [398].
Coherence	Evidence is predominantly based on animal stream
Experimental evidence	• There has been no experimental evidence generated from human studies. • Evidence is predominantly based on animal experimental studies
Analogy	No suitable analogies identified

Strength of association

Study	Effect estimates	Statistical Significance	Effect on male reproduction	Population
Bai 2020 [41]	• Compared with subjects at the first tertile of plasma fluoride, percent changes (95% CI) in testosterone were: ○ Second tertile: –8.08% (–17.36%, 2.25%) ○ Third tertile: –21.65% (–30.44%, –11.75%) • Male adolescents at the third tertile of plasma fluoride had decreased levels of testosterone: –21.09% (–36.61% to –1.77%). • Similar inverse associations were also found when investigating the relationships between plasma fluoride and estradiol. • Decreased levels of SHBG associated with water and plasma fluoride ○ Male adolescents (third tertile): –9.39% (–17.25% to –0.78%) ○ Female children (second tertile): –10.78% (–17.55% to –3.45%)	P trend <0.001	Inverse	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on male reproduction	Population
	Sex steroid hormones in serum	<0.001		
	• **Testosterone (ng/dL)** ○ Total: 28.74 (26.11, 31.37) ○ Male children: 4.48 (4.01, 4.95) ○ Male adolescents: 281.91 (258.56, 305.26) ○ Female children: 5.32 (4.96, 5.68) ○ Female adolescents: 23.80 (22.71, 24.89)			
	• **Estradiol (pg/mL)** ○ Total: 12.22 (11.35, 13.08) ○ Male children: 2.30 (2.23, 2.37) ○ Male adolescents: 15.02 (13.93, 16.11) ○ Female children: 4.89 (4.33, 5.45) ○ Female adolescents: 49.32 (45.15, 53.48)	<0.001		
	• **SHBG (nmol/L)** ○ Total: 55.27 (52.90, 57.63) ○ Male children: 89.91 (84.42, 95.40) ○ Male adolescents: 34.69 (32.62, 36.77) ○ Female children: 77.09 (71.35, 82.82)	<0.001		

Study	Effect estimates	Statistical Significance	Effect on male reproduction	Population
	○ Female adolescents: 54.01 (50.78, 57.25)			
An 2019 [55]	**Water fluoride (Mean ± SD)** • Group of villages with high exposure (HEG): 2.44±1.88 mg/L • Group of villages with low exposure (LEG): 0.37± 0.15 mg/L		Inverse	Adults
	Urinary fluoride (Mean ± SD), mg/L • HEG: 2.66 ± 1.03 • LEG: 0.95 ± 0.31	P = <0.001		
	Reproductive hormones (Mean ± SD), nmol/L			
	ABP • HEG: 19.86 ± 22.46 • LEG: 24.04 ± 26.94	P = 0.144		
	SHBG • HEG 30.07 ± 28.32 • LEG 35.90 ± 28.58	P = 0.012		

Consistency

Study	Design	Country	Population	Time period
Bai 2020 [41]	Cross-sectional	USA	Children/ adolescents	2013–2016
An 2019 [55]	Cross-sectional	China	Adults (males)	2011-2012

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Experimental evidence

Selected animal studies (tier-1; medium to high quality) investigating male fertility

Animal model		F in DW (mg/L)	Significantly altered outcomes	D-R trend
Rat (237)	**(subchronic)**	0, 10, 50, 100	Sperm quality[xlvi], testicular 3β-HSDH, serum testosterone levels, histology of testis and counts of germ cells	Altered at all doses tested
Rat (238)	**(subchronic)**	0, 5, 110	Sperm quality[xlvii], serum testosterone and histology of testis	Altered at all doses tested
Mice (211)	**(subchronic)**	0, 11, 22, 45	Sperm quality[xlviii], serum testosterone and histology of testis	Altered at all doses tested
Mice (924)	**(subchronic)**	0, 11, 22, 45	Ultra-structure of testicular tissues[xlix] and mitophagy in Leydig cells	Altered at all doses tested
Mice (925)	**(subchronic)**	0, 11, 22, 45	Testicular morphology and ultrastructure of sperm	Altered at higher doses
Mice (1595)	**(subchronic)**	0, 13, 32, 68	Sperm quality[l], hyperactivation and [Ca^{2+}] levels	Altered at higher doses

[xlvi] Total Sperm Count, Motility, and Abnormality

[xlvii] Sperm motility and abnormality

[xlviii] The sperm count, the abnormal ratio of sperm and sperm head

[xlix] Mitochondrial structural impairment in germ cells, Sertoli cells and Leydig cells

[l] Sperm motility, count and survival

Mice (subchronic) (1596)	0, 13, 32, 68	Sperm abnormalities and DNA integrity	Altered at higher doses
Mice (subchronic) (1718)	0, 22, 45, 68	Gonad weights, sperm quality[li]	Altered at higher doses
Mice (chronic) (1759)	0, 11, 22, 45	Sperm quality and histology of testis	Altered at all doses tested
Mice (chronic) (1799)	0, 11, 22, 45	Sperm quality[lii] and histology of testis	Altered at higher doses

[li] Sperm count, viability and morphology

[lii] Sperm count, motility and viability

Supplementary Material 8. Point of departure derivation

This supplement provides more information and technical detail on statistically deriving the POD for dental fluorosis. A list of extant international health-based values is provided. A re-analysis of the data published by Dean (1942) with dose-response modelling to derive a POD to protect against moderate and severe dental fluorosis is presented. The rationale for not deriving PODs for thyroid dysfunction, kidney dysfunction, and sex hormone disruptions is given. For cognitive IQ reductions in children, results from meta-analyses of NTP and the benchmark dose modelling of Grandjean et al. (2022) [399] are discussed. The conversion of urinary benchmark concentrations to drinking water concentrations to estimate the POD for fluoride based on the modeling results of Grandjean and colleagues is described. Issues for consideration in selecting the most appropriate endpoint for setting a health-based value for fluoride in drinking water are discussed.

8.1. HBV and MAC values reported by different authoritative agencies

The following table presents a selection of international HBV and MAC for fluoride in drinking water. These guidelines were based on considerations of the beneficial prevention of dental caries and the protection against dental fluorosis (as the most appropriate endpoint). The selection of candidate endpoints in the current review and the derivation of points of departure in a subsequent section were based on a review of all other health endpoints, excluding dental fluorosis.

Country / Organization	Reference Values	Source
WHO	"The guideline value for fluoride in drinking-water is 1.5 mg/L, based on increasing risk of dental fluorosis at higher concentrations and that progressively higher levels lead to increasing risks of skeletal fluorosis. This value is higher than that recommended for artificial fluoridation of water supplies for prevention of dental caries, which is usually 0.5–1.0 mg/L." (p. 3)	**WHO 2019** [400]

Country / Organization	Reference Values	Source
Canada	"… the optimal concentration of fluoride in drinking water for dental health has been determined to be 0.7 mg/L for communities who wish to fluoridate." (p. 2) "The maximum acceptable concentration (MAC) for fluoride in drinking water is 1.5 mg/L … Mild and very mild dental fluorosis are not considered to be adverse effects, whereas moderate dental fluorosis is found to be an adverse effect, based on its potential cosmetic concern, and is used as the endpoint of concern in the risk assessment used to establish the Maximum Acceptable Concentration." (p. 1) "Health Canada has calculated a health-based value of 0.9 mg/L for fluoride in drinking water, which is deemed protective against any potential adverse health effect from fluoride." (p. 64)	**Health Canada 2010** [1].
USA	"For community water systems that add fluoride to their water, PHS recommends a fluoride concentration of 0.7 mg/L (parts per million [ppm]) to maintain caries prevention benefits and reduce the risk of dental fluorosis." (p. 319)	**U.S. Department of Health and Human Services 2015** [401]
	"The current enforceable drinking water standard for fluoride is 4.0 mg/L. This is the maximum amount that is allowed in water from public water systems. It is set to meet the current public health goal for protection against increased risk of crippling skeletal fluorosis, a condition characterized by pain and tenderness of the major joints." (p. 2) "EPA also has a non-enforceable secondary standard for fluoride of 2.0 mg/L, which is recommended to protect children against the tooth discoloration and/or pitting that can be caused by excess fluoride exposures during the formative period prior to eruption of the teeth. Although water systems are not required to comply with secondary standards, for fluoride, EPA does require that systems notify customers if the average water levels exceed the secondary standard." (p. 2 – 3)	**US Environmental Protection Agency 2011** [402]

Country / Organization	Reference Values	Source
Australia	"Based on health considerations, the concentration of fluoride in drinking water should not exceed 1.5 mg/L." (p. 668) "The guideline value of 1.5 mg/L has been set to protect children from the risk of dental fluorosis." (p. 669)	**National Health and Medical Research Council, Australia 2021** [100]
	"NHMRC supports Australian states and territories fluoridating their drinking water supplies within the range of 0.6 to 1.1 mg/L. This range is aimed at reducing tooth decay, while avoiding any occurrence of dental fluorosis of aesthetic concern. In each Australian state or territory, the government health authority determines the appropriate operational levels within the range of 0.6 to 1.1 mg/L." (p. 1)	**National Health and Medical Research Council, Australia 2017** [100]
Ireland	"Community water fluoridation at a level of 1 ppm began in Ireland in 1964 as a measure to prevent dental caries. A major review of Ireland's water fluoridation policy in 2002 showed an increasing occurrence of dental fluorosis. As a result, in 2007, the fluoride level in drinking water in Ireland was lowered to a range of 0.6 to 0.8 ppm, with a target of 0.7 ppm. This remains the target and range applied in Ireland today." (p. 6)	**Sutton et al. 2015** [403]
	"In Europe, the maximum level of fluoride currently allowed in drinking water is 1.5 parts per million (ppm) (2). However, in Ireland, the 1960 Health (Fluoridation of Water Supplies) Act restricts the maximum level of fluoride to only 1ppm and this supersedes the European maximum limit." (p. 18)	**Food Safety Authority of Ireland 2006** [404]
New Zealand	"The NZMoH [New Zealand Ministry of Health] recommends that, for oral health reasons, the level of fluoride in drinking water in New Zealand should be between 0.7 and 1.0 mg/L. Based on WHO advice, the maximum acceptable value for fluoride in drinking water is 1.5 mg/L to prevent any known adverse health effects (dental or skeletal fluorosis)." (p. 22)	**Royal Society of New Zealand 2014** [405]

8.2. Derivation of a point of departure for moderate dental fluorosis

Methodology

In its 2010 report [406] entitled *Fluoride: Dose-Response Analysis For Non-cancer Effects*, the US EPA performed a dose-response analysis on severe dental fluorosis as a function of fluoride in drinking water. The dose-response analysis was conducted using the dataset from Dean (1942) [407]. Five models were fit to the data (log Probit model, Probit model, log logistic model, logistic model, and dichotomous Hill model) with the dichotomous Hill model as the preferred model based on its AIC value (see Table 4-2 from EPA (2010) [406]). The resulting benchmark dose (BMD) for 1% severe dental fluorosis was 2.43 mg/L, while the corresponding lower bound of the benchmark dose (BMDL) was found to be 2.18 mg/L. It should also be noted that US EPA [406] attempted to fit these models to data on moderate dental fluorosis; however, none of the models provided an acceptable model fit to derive benchmark dose using the selected analytic strategy.

Identification of the key study

As described above in the systematic review methods and results sections, a bibliographic search was conducted for all epidemiologic studies on fluoride in drinking water and dental fluorosis. The review was an update of the CADTH (2019) systematic review. However, in considering whether there existed a preferable study to Dean (1942) [407], candidate key studies were considered from all studies published after 1942. The selection of a preferable key study involved several considerations: the study would have a low risk of bias based on its design and analytic methodology, there would be data adequate for a dose-response analysis of moderate dental fluorosis, the design of the study would not be entirely ecologic (that is, aggregate statistics) to allow for proper inference, other sources of fluoride would ideally be considered, the study would be based on a child or adolescent study population, ideally drinking water fluoride levels would be reflected in a range that includes levels below 0.7 ppm, the study

size would be sufficiently large for dose-response modelling, and the study setting would offer natural parallels to a North American context. The team did not further consider studies published before 2008 (as the US EPA had already reviewed these in detail). Risk of bias of studies published after 2008 were based on assessments conducted by Iheozor-Ejiofor et al 2015 [106] and CADTH 2019 [2], and within the current review.

Epidemiologic studies published to date were of variable risk of bias levels, particularly based on concerns for exposure assessment and potential confounding, among other issues. A major consideration was that other sources of fluoride (such as dental cleaning products and rinses) are common in more recent eras. This poses considerable uncertainty in dose-response modelling of the effects of fluoride in drinking water, as was also noted by the US EPA (2008) [406] . At the time of its review, the US EPA also preferred Dean (1942) [407] because it used a standardized protocol to assess dental fluorosis, had a relatively large study size, and had a requirement for continuous residency of the children participating in the study. As no candidate key studies were identified, for the reasons described above, Dean (1942) [407] was still preferred for statistical modeling purposes.

Dataset

Dean (1942) [407] was a cross-sectional study for 5824 children, in 22 cities across 10 states of the U.S. The children were 9-19 years old or in grades 2-12, depending on the township where they resided. The design was comprised of a comparison of regions with varying water fluoride levels. Drinking water was the only route of exposure considered in the study. Dental fluorosis was measured using Dean's Index. Community fluoride concentrations were based on the Elvove (1933) [408] method, derived from the mean of twelve-monthly samples.

The data used for the dose-response analysis is summarized in Table 10, which is generated by aggregating from Dean (1942) [407] and sorting by the fluoride concentration levels in the drinking water supplies. The number of moderate (DFI=3) or severe (DFI=4) dental fluorosis cases for each community is calculated by combining proportions of moderate and severe dental fluorosis and multiplying by the number of study participants in each town.

The US EPA (2010) [406] argued that data from the town of Bauxite, AR, was an outlier, with a confounding factor of the excessive amounts of alumina in the environment due to the 1494

aluminum mine and smelter in the region. Therefore, data for Bauxite (26 children at an exposure level of 14.1mg/L) is excluded from the present analysis.

Table 10: Fluoride concentration in drinking water supplies and number of cases of moderate/ severe dental fluorosis (modified from Dean, 1942)

Town	State	Sample size	Age (Years)	F (mg/L)	Cases (Moderate + Severe)
Waukegan	IL	423	12-14	0	0
Michigan City	IN	236	12-14	0.1	0
Zanesville	OH	459	12-14	0.2	0
Lima	OH	454	12-14	0.3	0
Marion	OH	263	12-14	0.4	0
Elgin	IL	403	12-14	0.5	0
Pueblo	CO	614	12-14	0.6	0
Kewanee	IL	123	12-14	0.9	0
Aurora	IL	633	12-14	1.2	0
Joliet	IL	447	12-14	1.3	0
Elmhurst	IL	170	12-14	1.8	2
Galesburg	IL	273	12-14	1.9	3
Clovis	NM	138	9-11	2.2	16
Colorado Springs	CO	404	12-14	2.6	42
Plainview	TX	97	9-12	2.9	26
Amarillo	TX	289	9-13	3.9[1]	136
Conway	SC	59	9-14	4	21
Lubbock	TX	189	9-15	4.4	121
Post	TX	38	~8-11[3]	5.7[2]	34
Chetopa	KS	65	~7-17[4]	7.6[2]	45
Ankeny	IA	21	~6-17[5]	8.0[2]	19
Bauxite	AR	26	14-19	14.1[2]	24

[1] *"Subject to possible correction to 4.2mg/L during susceptible period of age group examined." (Dean, 1942)*

[2] *Those observations are based on a single determination. Others are calculated as the average of samples across 12-month timeline.*

[3] *Corresponds to children in grades 4 to 6*

[4] *Corresponds to children in grades 3 to 12*

[5] *Corresponds to children in grades 2 to 12*

Bayesian vs. frequentist dose-response modelling

As mentioned in the US EPA (2010) report [406], none of the models used in the dose-response modelling on the moderate and severe dental fluorosis provided acceptable fit to the data. For the current review, a Bayesian framework was employed for the benchmark dose estimation using the more recently available Benchmark BMD software (BBMD) developed by Shao and Shapiro (2018) [409]. This approach would in principle provide improved model fit to a given dataset. Briefly, the Bayesian analysis calculates the posterior probability for parameter set $\boldsymbol{\theta}$ given data (i.e., $p(\boldsymbol{\theta}|\mathrm{Data})$) as

$$p(\boldsymbol{\theta}|\mathrm{Data}) \propto \pi(\boldsymbol{\theta})L(\mathrm{Data}|\boldsymbol{\theta}) ,$$

where $\pi(\boldsymbol{\theta})$ denotes the prior distribution for $\boldsymbol{\theta}$, $L(\mathrm{Data}|\boldsymbol{\theta})$ represents the likelihood function. In particular, since the data is dichotomous (i.e., “success” if a study participant exhibits moderate or severe dental fluorosis, or “failure” otherwise), the likelihood function can be described using binomial distribution.

$$L(\mathrm{Data}|\boldsymbol{\theta}) = \prod_{i=1}^{I} \binom{n_i}{y_i} p(d_i|\boldsymbol{\theta})^{y_i}[1 - p(d_i|\boldsymbol{\theta})]^{n_i - y_i} ,$$

where n_i represents the number of participants in each exposure group, and y_i corresponds to number of participants developing moderate or severe dental fluorosis in ith exposure group, and $p(d_i|\boldsymbol{\theta})$ is the probability of developing moderate or severe dental fluorosis given exposure concentration at ith group. For all analyses, to derive a BMD and POD to protect against moderate dental fluorosis, a DFI cutoff of 3+ was used for modelling (i.e., a combination of moderate (DFI=3) and severe (DFI=4) categories, as described in Dean (1942) [407]).

There are a number of plausible dose-response model that can be used for the analysis. In particular, the BBMD software provides eight models available for the dose-response analysis to fit dichotomous data:

- Quantal linear model
- Probit model
- Logistic model
- Weibull model
- Multistage (2nd order) model
- Log logistic model
- Log Probit model
- Dichotomous Hill model

All eight models provided by the BBMD software were used for the dose-response analysis; however, only log logistic, log Probit, and dichotomous Hill models provided convergence and adequate fit for the analysis. These three models, as well as the prior distributions for corresponding model parameters are shown below.

Log logistic model

$$f(d) = a + \frac{1-a}{1+e^{-(c+b\times\log(d))}},$$

where the prior distributions for the parameters are given by: $a \sim Uniform(0,1)$; $b \sim Uniform(1,15)$; and $c \sim Uniform(-5,15)$.

Log Probit model

$$f(d) = a + (1-a) \times \Phi(c + b \times \log(d)),$$

where the prior distributions for the parameters are given by: $a \sim Uniform(0,1)$; $b \sim Uniform(1,15)$; and $c \sim Uniform(-5,15)$.

Dichotomous Hill model

$$f(d) = a \times g + \frac{a(1-g)}{a + e^{-(c+b\times\log(d))}},$$

where the prior distributions for the parameters are given by: $a \sim Uniform(0,1)$; $b \sim Uniform(1,15)$; $c \sim Uniform(-5,15)$; and $g \sim Uniform(0,1)$.

For the prior distributions for all parameters, the uniform distribution with the default lower and upper bounds are used. These default values were chosen based on the biological considerations [409]. See section 2 of the supplemental material from Shao and Shapiro (2018) [409] for the details of the remaining models.

Benchmark-dose modelling of added and extra risks

The objective of the dose-response analysis conducted in this section is to derive a point-of-departure (POD) using the BMD and the BMDL. The added-risk and extra-risk-based BMDs, for a prespecified benchmark response (BMR), can be defined as

$$\mathrm{BMD}_{\mathrm{ad}} = \{d : f(d) - f(0) = \mathrm{BMR}\},$$

and

$$\mathrm{BMD}_{\mathrm{ex}} = \left\{d : \frac{f(d) - f(0)}{1 - f(0)} = \mathrm{BMR}\right\},$$

where $f(d)$ and $f(0)$correspond to the risk of developing moderate or severe dental fluorosis at exposure levels d and 0, respectively.

Choice of benchmark response

Derivation of BMD and BMDL estimates were based on the extra-risk BMR of 1%, 5%, and 10%, given that extra-risk based BMR would always produce an estimate less than or equal to the BMD based on added risk.

Adequacy of model fit

As in classical (i.e., frequentist) statistics, the model fit to the data can be checked for adequacy in the Bayesian analysis. One such measure is called the posterior predictive p-value (PPP). The PPP indicates the discrepancy between the observed data and the plausibility of generating the observed data based on the posterior predictive distribution. If the model's PPP value is between 0.05 and 0.95, the model's fit it thought to be adequate. For a more detailed explanation of the PPP, see Gelman (2013) [410].

Model selection and model averaging

When there is more than one plausible model to describe the dose-response relationship, there would be more than one BMD estimate derived. There are two ways to determine a single "best" BMD estimate from a set of BMDs. One way is to choose the BMD from the most plausible model (model selection), and another way is to calculate the weighted average of the BMD estimates (model averaging). Either way, such determination requires the use of posterior model weights.

First, assume that equal prior model weights are assigned to each of candidate model, as there is no reason to believe one model is more plausible than others. Consequently, the model weight [411] for the jth model can be calculated as

$$\widehat{m}_j = \exp\left(\hat{l}_j - \frac{d_j}{2} log(n)\right),$$

where $\hat{l}_j$ denotes the estimated log-likelihood value, d_j represents the number of parameters used in jth model, with sample size represented by n. Therefore, using equal prior model weights, the posterior model weight for each of the model included in model selection/averaging can be calculated as

$$\widehat{pm}_j = \frac{\widehat{m}_j}{\sum_{t=1}^{T} \widehat{m}_t},$$

and therefore, the BMD estimate for model selection is given by

$$\widehat{\mathrm{BMD}}_{MS} = \underset{\widehat{pm}_j}{\mathrm{argmax}}\, \widehat{\mathrm{BMD}}_j .$$

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Similarly, the BMD estimate for the model averaging is given by

$$\widehat{\mathrm{BMD}}_{MA} = \sum_{t=1}^{T} \widehat{pm}_t \times \widehat{\mathrm{BMD}}_j \, .$$

Results

NOAEL and LOAEL

Although the purpose of this section is to determine the POD based on BMD, it is worthwhile noting that the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) for the moderate or severe dental fluorosis are 1.3 mg/L and 1.8 mg/L, respectively. The LOAEL corresponds to a 1.2% positivity rate in the study participants from Elmhurst, IL (when all communities in Dean (1942) [407] are sorted by fluoride concentration, the lowest concentration at which moderate dental fluorosis manifests is within the Elmhurst community, which had 1.8 ppm F concentration).

BMD estimates based on individual models

Dose-response analysis using log logistic model

Figure 1 shows the estimated dose-response curve using log logistic model. With the PPP value of 0.453, there is no reason to believe the inadequacy of the model fit. The estimated BMD and BMDL based on extra-risk based BMR of 1%, 5%, and 10% are presented in Table 11. When the BMR is set to 1%, the BMD and BMDL estimates are 1.45 mg/L and 1.35 mg/L, respectively. The estimated model weight for log logistic model is less than 0.001%, indicating that, of the three models used in this analysis, log logistic model has the lowest loglikelihood.

It should also be noted that, as the estimated background risk of developing moderate or severe dental fluorosis is 2.4×10^{-4} (Table 12), the added-risk based BMD and BMDL estimates would be the same as those shown in Table 11. The parameter estimates given in Table 12 uses the normalized exposure levels. In short, exposure levels in all data sets are normalized to the scale between 0 to 1 by dividing the exposure level d by the maximum exposure level ($8.0 mg/L$) from the study.

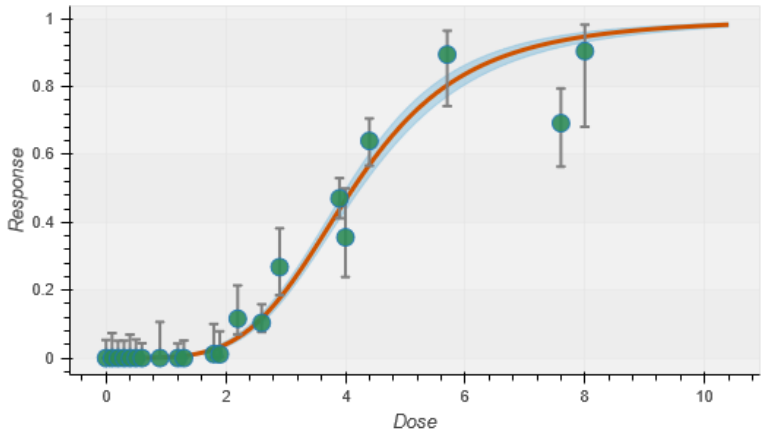

Figure 1: Estimated dose-response curve using log logistic model (orange line), with 90% confidence interval shown in light blue shade.

(Green dots represent the observed data while the vertical bars denote the 90% confidence interval about the observation.)

Table 11: Estimated BMD and BMDL values based on log logistic model. The extra-risk based BMR are used.

BMR	Log Logistic Model	
	BMD (mg/L)	BMDL (mg/L)
1%	1.45	1.35
5%	2.11	2.01
10%	2.50	2.41

Table 12: Estimated parameters for log logistic model.

Parameter	Log Logistic model		
	Mean	SE(Mean)	Standard Deviation
$\boldsymbol{a}$	2.4×10^{-4}	2.0×10^{-6}	2.4×10^{-4}
$\boldsymbol{b}$	4.38	2.1×10^{-3}	0.2
$\boldsymbol{c}$	2.9	1.9×10^{-3}	0.18
$\boldsymbol{lp}$	-737.6	0.01	1.27

Dose-response analysis using log Probit model

Figure 2 shows the estimated dose-response curve using log Probit model. With the PPP value of 0.396, there is no reason to believe the inadequacy of the model fit. Table 13 summarizes the estimated BMD and BMDL based on extra-risk based BMR of 1%, 5%, and 10%. When the BMR is set to 1%, the BMD and BMDL estimates are 1.58 mg/L and 1.49 mg/L, respectively. The estimated model weight for log Probit model is 0.046%, implying that log Probit model is a more plausible underlying model than the log logistic model for describing dose-response relationship between fluoride concentration in drinking water and development of moderate or severe dental fluorosis.

Similar to the log logistic model, as the estimated background risk of developing moderate or severe dental fluorosis is 2.4×10^{-4} (Table 14), the added-risk based BMD and BMDL estimates would be the same as those shown in Table 13. Note also that the parameter estimates given in Table 14 uses the normalized exposure levels.

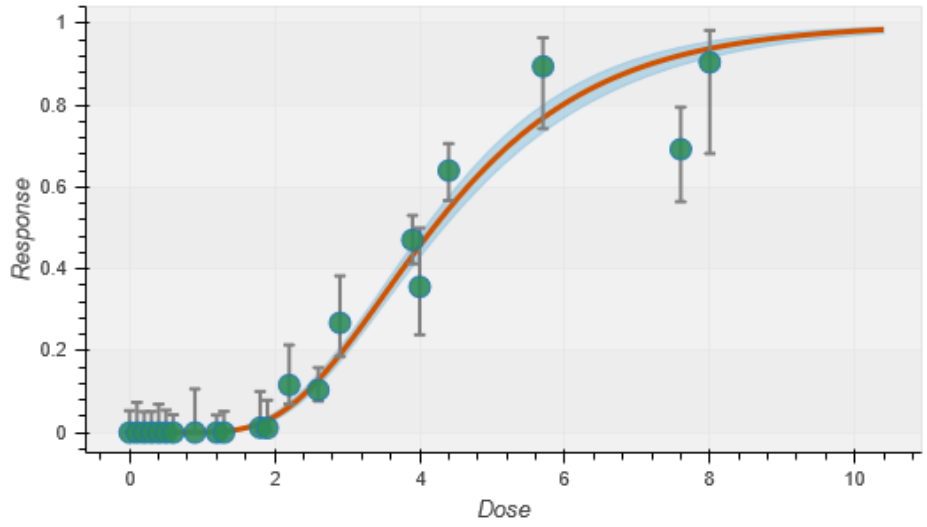

Figure 2: Estimated dose-response curve using log Probit model (orange line), with 90% confidence interval shown in light blue shade.

(Green dots represent the observed data while the vertical bars denote the 90% confidence interval about the observation.)

Table 13: Estimated BMD and BMDL values based on log Probit model. The extra-risk based BMR are used.

BMR	Log Probit Model	
	BMD (mg/L)	BMDL (mg/L)
1%	1.58	1.49
5%	2.10	2.02
10%	2.45	2.37

Table 14: Estimated parameters for log Probit model.

Parameter	Log Probit Model		
	Mean	SE(Mean)	Standard Deviation
a	2.4×10^{-4}	2.0×10^{-6}	2.4×10^{-4}

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$\boldsymbol{b}$	2.38	1.1×10^{-3}	0.10
$\boldsymbol{c}$	1.5	1.0×10^{-3}	0.10
$\boldsymbol{lp}$	-732.5	0.01	1.29

Dose-response analysis using dichotomous Hill model

Figure 3 shows the estimated dose-response curve using log logistic model. With the PPP value of 0.452, there is no reason to believe the inadequacy of the model fit. As shown in Figure 3, the dichotomous Hill model plateaus at 78% response rate, meaning that the Hill model assumes that even as fluoride concentration increase infinitely, only about 78% of population would develop either moderate or severe dental fluorosis. The estimated BMD and BMDL based on extra-risk based BMR of 1%, 5%, and 10% are presented in Table 15. When the BMR is set to 1%, the BMD and BMDL estimates are 1.66 mg/L and 1.56 mg/L, respectively, which are slightly larger than those based on the log logistic and the log Probit models. When considering the model averaging results, the estimates were heavily weighted toward those of the Hill model (with an estimated model weight of 99.95%).

The background rate for the Hill model is given by $(a \times g)$. From Table 16, we obtain that $a \times g = 2.5 \times 10^{-4}$, and therefore the added-risk based BMD and BMDL estimates for the Hill model are identical to those presented in Table 15. Note also that the parameter estimates given in Table 16 uses the normalized exposure levels.

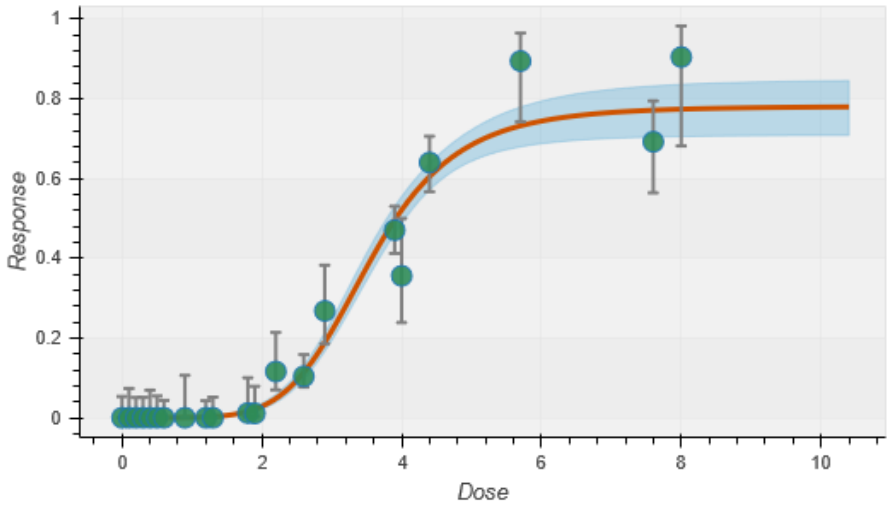

Figure 3: Estimated dose-response curve using dichotomous Hill model (orange line), with 90% confidence interval shown in light blue shade.

(Green dots represent the observed data while the vertical bars denote the 90% confidence interval about the observation.)

Table 15: Estimated BMD and BMDL values based on dichotomous Hill model. The extra-risk based BMR are used.

BMR	Dichotomous Hill Model	
	BMD (mg/L)	BMDL (mg/L)
1%	1.66	1.56
5%	2.22	2.13
10%	2.53	2.46

Table 16: Estimated parameters for dichotomous Hill model.

	Dichotomous Hill Model		
Parameter	**Mean**	**SE(Mean)**	**Standard Deviation**
a	0.78	4.3×10^{-4}	0.04
b	5.77	4.3×10^{-3}	0.38
c	4.71	5.3×10^{-3}	0.46
g	3.2×10^{-4}	2.5×10^{-6}	3.2×10^{-4}
lp	-732.5	0.01	1.29

BMD estimates using model averaging

In the previous section, based on estimated model weights and fit statistics, the Hill model may be the single most plausible model to describe the dose-response relationship based on the data from Dean (1942) [407]. Since there always is an uncertainty about which model is the "true" model, it may be beneficial to adjust the BMD and BMDL estimates by taking the weighted average of the BMD estimates from different models. As shown in Table 17, the BMD and BMDL estimates based on model averaging is identical to those of the Hill model. This is because the model weight for the Hill model is 99.95%. Therefore, whether model averaging or model selection is used, the BMD and BMDL estimates corresponding to 1% BMR would be 1.66 mg/L and 1.56 mg/L, respectively.

Table 17: Estimated BMD and BMDL values by model averaging. The extra-risk based BMR are used.

BMR	Model Averaging	
	BMD (mg/L)	**BMDL (mg/L)**
1%	1.66	1.56
5%	2.22	2.13
10%	2.53	2.46

Sensitivity analysis

Effect of correction in exposure

As stated in the footnote on Table 10, Dean (1942) [407] indicated the exposure level in Amarillo, TX, may be subject to a possible correction to 4.2 mg/L (instead of 3.9 mg/L) "during susceptible period of age group examined". Although the age group of study participants from Amarillo does not seem to differ greatly from children from other communities, a sensitivity analysis was performed with a modified fluoride concentration for the Amarillo subjects.

The BMD and BMDL estimates under the log logistic, log Probit, and Hill models, as well as from model averaging are provided in Table 18. As expected, these estimates are very similar to those from the original analysis (Table 11, Table 13, Table 15, and Table 17). In particular, BMD and BMDL estimates for 1% extra risk based on model averaging are 1.63 mg/L and 1.52 mg/L, respectively.

Table 18: BMD and BMDL estimates under various models. The exposure level for Amarillo, TX, has been modified to 4.2 mg/L for possible susceptible period of age group examined, as noted by Dean (1942).

BMR	Log logistic Model		Log Probit Model		Dichotomous Hill Model		Model Average	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
1%	1.63	1.52	1.44	1.34	1.58	1.49	1.63	1.52
5%	2.21	2.12	2.13	2.04	2.12	2.03	2.22	2.12
10%	2.55	2.46	2.54	2.45	2.48	2.39	2.55	2.46

Effect of higher concentration groups

The Hill model provided the best fit in the main analysis. This may be due to the extra parameter in the Hill model that allows for the model to plateau before reaching a 100% incidence rate. To investigate the effect of the plateauing effect on the estimation of BMD, two additional analyses were considered, where the highest concentration group (i.e., Ankeny, IA at 8.0 mg/L) and two highest concentration groups (i.e., Ankeny, IA, and Chetopa, KS at 7.6 mg/L) are removed. The BMD estimates based on these additional analyses are presented in Table 19 and Table 20.
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When only the highest concentration group is excluded, the resulting model average BMD and BMDL estimates are nearly identical to those found in the original analysis (1.68 mg/L vs. 1.66 mg/L for BMD, and 1.57 mg/L vs. 1.56 mg/L for BMDL for 1% BMR). When the two highest exposure groups are excluded, the model average BMD estimates are slightly increased at 1.72mg/L for 1% BMR. Although the BMD estimates are mostly unaffected by the plateauing effect, when both Ankeny and Chetopa subjects were excluded from the analysis, the log Probit model became the dominant dose-response model (with the model weight of 91.2%). This indicates that the model fit may be heavily influenced by the plateauing effect (i.e., whether incidence rate will become 100% as exposure increase or not), and therefore it would be preferable to use the BMD and BMDL estimates from model averaging, rather than using only the most plausible model.

Table 19: BMD and BMDL estimates under various models. The highest exposure group (Ankeny, IA) is excluded from this dose-response analysis.

BMR	Log logistic Model		Log Probit Model		Dichotomous Hill Model		Model Average	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
1%	1.45	1.35	1.58	1.49	1.68	1.57	1.68	1.57
5%	2.11	2.02	2.1	2.02	2.22	2.13	2.22	2.13
10%	2.50	2.42	2.45	2.37	2.53	2.45	2.53	2.45

Table 20: BMD and BMDL estimates under various models. The two highest exposure groups (Ankeny, IA, and Chetopa, KS) are excluded from this dose-response analysis.

BMR	Log logistic Model		Log Probit Model		Dichotomous Hill Model		Model Average	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
1%	1.60	1.50	1.72	1.63	1.63	1.52	1.72	1.59
5%	2.21	2.12	2.2	2.11	2.22	2.13	2.2	2.11
10%	2.57	2.48	2.5	2.42	2.55	2.47	2.51	2.43

Conclusion

The dose-response analysis using data from Dean (1942) [407] was performed to investigate the relationship between the fluoride concentration in drinking water and the development of moderate or severe dental fluorosis. The model average benchmark dose for 1% extra-risk and corresponding BMDL were determined to be 1.66 mg/L, and 1.56 mg/L, respectively. These values are slightly less than the LOAEL (1.8 mg/L), which had the positivity rate of 1.2% in the study population. Although three models were used to derive the model average BMD, the Hill model was the dominant model with a 99.95% model weight.

There were some uncertainties in some of the collected data. For example, Dean (1942) suggested that a potential correction for the exposure level for the town of Amarillo may be needed. A sensitivity analysis with modified data suggested that the 1% BMD and BMDL are slightly decreased at 1.62mg/L and 1.53mg/L, respectively. Another sensitivity analysis was performed to investigate the impact of plateauing effect on the BMD estimates. When two of the highest exposure groups were excluded, the BMD and BDML estimates increased slightly, to 1.72 mg/L and 1.59 mg/L. Although the BMD estimates were stable, removal of highest concentration groups led to a change in the dominant model (log Probit model had model weight of 91.2%), indicating that the BMD estimation should be based on model averaging rather than model selection.

8.3. Derivation of points of departure for other candidate endpoints

The selection of candidate endpoints in the current review and the derivation of points of departure in a subsequent section were based on a review of all other health endpoints, excluding dental fluorosis. See Section 8.1 above for a summary of a selection of international HBV and MAC for fluoride in drinking water. These guidelines were based on considerations of the beneficial prevention of dental caries and the protection against dental fluorosis (as the most appropriate endpoint).

Cognition, IQ

The body of evidence considered in the current review suggests a positive association of reduced IQ scores for children and fluoride exposures relevant to current North American drinking water levels. Using the 2022 NTP dose-response mean-effects meta-analysis [104] of 29 human epidemiologic studies with aggregate-level exposure measurement, the linear dose-response model resulted in a change (a reduction) in IQ of -0.15 (standardized mean difference (SMD), 95% CL: −0.20, −0.11) between the drinking water fluoride exposed group and the reference group within each study.

Restricting the dose-response meta-analysis to those studies that included an exposed (non-reference) group with mean fluoride concentrations below 1.5 mg/L (7 studies contributed 7 observations to the dose-response estimate) resulted in an estimate of the change in IQ of 0.05 (standardized mean difference, 95% CL: -0.36, 0.45) between the exposed group and the reference group using a linear model. This latter result could be used as evidence to reconsider the HBV for fluoride in drinking water in Canada; however, the estimate was based on largely cross-sectional studies with high risk of bias, including lack of adjustment for effects of other contaminants, such as arsenic and lead.

The 2022 NTP draft [104] also includes a mean effects meta-analysis, with studies that reported sex-stratified results (14 studies of boys, 13 studies of girls) with these subgroup analyses resulting in IQ changes of (SMD) −0.62 (95% CI: −0.81, −0.42) in boys and −0.53 (95% CI: −0.72, −0.34) in girls. The 2022 NTP draft [104] includes a regression slopes meta-analysis of epidemiologic studies with individual-level fluoride exposure measures (including several cohort studies) with an estimated -4.77 IQ point change for a 1-mg/L increase in water fluoride (β = −4.77; 95% CI: −9.09, −0.45) and -1.81 (-2.80, -0.81) for urinary fluoride.

Benchmark dose (BMD) modelling results have been recently published, based on high-quality birth cohort data. Grandjean and colleagues [399] conducted a BMD analysis using the pooled MIREC and ELEMENT cohorts, with assessment of maternal urinary fluoride levels. The MIREC North American cohort (Maternal–Infant Research on Environmental Chemicals) was the basis of previous assessments of prenatal fluoride exposure and childhood IQ ([53, 101] and) and the ELEMENT longitudinal birth cohort (Early Life Exposures in Mexico to Environmental

Toxicants) was used to assess maternal and fetal fluoride exposure and childhood IQ in a Mexican population [85].

The combined cohort represents high quality evidence partly based on a North American population, conducted within a context relevant to North American drinking water fluoride exposure levels. Both studies included prospective data collection, with prenatal exposure assessment (maternal urine collection over successive trimesters) and follow-up during the early life of the infants and children. In risk of bias assessments conducted by NTP, the earlier publications by [53, 85, 101] were assessed at low risk of bias due to unlikely concerns from measurement error on cognition and urine F concentration, selection of study samples, and confounding adjustment from known factors [These assessments are relevant to the publication by Grandjean et al. [399], which used the same data sources].

Exposure coverage in the cohort reflects (urinary) fluoride levels below the current health-based value of 0.9 mg/L for fluoride in drinking water (with Grandjean reporting the mean urinary fluoride concentration [creatinine-adjusted] among pregnant women was 0.89 mg/L in Mexico City and 0.84 mg/L in Canada). Regression modelling by Grandjean et al. (2022) [399] included adjustment for critical confounders, including other chemical neurotoxicants in drinking water and socioeconomic impacts that would affect cognitive and mental health development. Adjustment included arsenic and lead exposures, as well as non-chemical determinants (gestational age, age at measurement, maternal education, race/ethnicity, child sex, parity, second-hand smoke, city, and quality of home environment [emotional support; cognitive stimulation]).

Stratified and models with interaction terms were include to the relationship between sex and urinary-fluoride exposure. In the BMD modelling, various regression models (linear, quadratic, segmented) were used to estimate the benchmark concentration for a benchmark response of a 1-point reduction in IQ. Model fits were similar but resulted in widely varying estimated benchmark concentrations, with some models for girls not converging.

At present, mode and mechanism of action information is insufficient to establish a preference for the linear or nonlinear models considered by Grandjean and colleagues [399]. Based on a benchmark response (BMR) of 1 IQ point and using the linear model results, the benchmark concentration (BMC) for maternal urinary fluoride (MUF) was 0.312 mg MUF/L, and the one-

sided lower limit of the BMC (the BMCL) was 0.192 mg MUF/L) when pooling General Cognitive Index (GCI) scores for the youngest children of both sexes in both cohorts. In sex-stratified results, estimated benchmark concentrations were lower in boys than in girls.

Results varied in the two cohorts and by age at measurement – but when pooled for the youngest aged children, the derived BMCL from the linear model for boys was 0.125 MUF/L and for girls was 0.315 MUF/L.

To derive a potential *BMCL for fluoride in drinking water* based on the maternal urinary results from the pooled analysis of the MIREC and ELEMENT cohorts conducted by Grandjean and colleagues [399] requires a conversion based on the following assumptions:

- Because of the uncertainty as to the shape of the dose-response curve at low concentrations of drinking water, the more stringent linear model, rather than the squared or break-point models considered by Grandjean and colleagues [399], was selected in order that the BMCL not be overestimated.
- For a BMR of 1 IQ point, the $BMCL_{MUF}$ was 0.192 mg MUF/L, based on the linear model results from Grandjean and colleagues for the pooled cohorts at younger ages
- Daily drinking water intake is 1.53 L/day (Health Canada default value).
- 24-hour fraction of fluoride excretion in adults is 0.75 [412]. This fractional urinary fluoride excretion (FUFE) is the ratio of fluoride excreted and fluoride ingested, FUFE = F_{excr}/F_{ing},
- F_{excr} is a product of urinary volume (over 24h) and the urinary fluoride concentration. A normal range of 24-hour urine volume is 800 to 1,200 mL,[liii] with 2 L of fluid intake per day. Given the mid-value of 1.4 L of urine volume per 2 L of fluid intake, and assuming linearity, the 24-hour urine volume for North Americans (with 1.53 L intake) would be 1.07 L.
- The susceptible population was young school-aged children, with the critical window of exposure being during prenatal periods and thus based on maternal intake.

Under these assumptions, the amount of fluoride ingested per day corresponding to the $BMCL_{MUF}$ is:

$$F_{ing} = [BMCL_{MUF} \times \text{24-hour urine volume}] / FUFE$$

[liii] Urine 24-hour volume Information | Mount Sinai - New York

= [0.192 mg/L x 1.07 L/d] / 0.75

= 0.274 mg/day

And the BMCL for fluoride in drinking water is then calculated as:

$BMCL_{DW}$ = F_{ing} / water intake

= (0.274 mg/day) / (1.53 L/day)

= 0.179 mg F/L[liv]

Grandjean and colleagues [399] fit different linear and non-linear models, which resulted in lower bounds of benchmark concentrations which differed by more than 9-fold (when converted to drinking water concentration, with the method described above, the variously derived BMCLs ranged from 0.077 mg F/L to 0.753 mg F/L drinking water).

The point of departure of 0.179 mg F/L from the combined high-quality cohorts stands in contrast to the 2022 draft NTP report conclusions that evidence for fluoride effects on cognitive function in children is less consistent below 1.5 mg F/L. In choosing between the BMCL of 0.179 mg F/L based on the more stringent model fit to the MIREC and ELEMENT cohorts by Grandjean and colleagues [399] , and a weight of evidence conclusion that evidence for neurological effects of fluoride in children below concentrations of 1.5 mg F/L was less consistent, consideration was also given to the quality of evidence.

While the BMCL derived from the cohort data suggests a much lower POD than 1.5 mg/L, the overall body of evidence suggests significant uncertainty in any low exposure-range derivation with current evidence. At this point in time, 1.5 mg/L may be considered as a provisional point of departure for establishing an HBV for fluoride in North American drinking water based on protection against neurocognitive effects in children. This POD should be reviewed as additional data accumulates on the biological mechanisms by which fluoride impacts cognitive function, providing additional insights into the shape of the exposure-response curve at lower concentrations.

[liv] The derivation of the drinking water BMCL was based on Grandjean et al 2022. Results from Villa et al 2004, assume that all fluoride ingested is via drinking water. They reported for their participants, about 75% of fluoride could be attributed to drinking fluids (but food, drinks, and toothpaste were all controlled in the study, and the study was conducted in Chile, which may be less applicable a North American Population).

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Thyroid dysfunction

The current review and weighing of evidence under Bradford Hill considerations provided reasonable credibility from generally low to acceptable risk of bias – albeit cross-sectional – human epidemiologic studies to suggest a possible association of fluoride exposure in North American drinking water contexts and effects on thyroid dysfunction. No study was considered adequate to derive a point of departure. In considering the animal stream of evidence, only 2 low risk of bias studies with dose-response information were considered relevant [210, 231]. Out of these 2 rat chronic studies, one study did not find a change in thyroid hormone levels (T3, T4, or TSH) at the highest test concentrations (20 ppm), and the other study did not consistently demonstrate significant change across time points. Overall, these studies were considered insufficient for derivation of a point of departure for thyroid-related effects in humans.

No point of departure was derived.

Kidney dysfunction

Epidemiologic human studies were broadly consistent on supporting a possible association of fluoride exposure in North American contexts and effects on kidney dysfunction, with weighing of evidence under Bradford-Hill considerations supportive of the association being possibly causal. However, all human studies were cross-sectional in design and were not considered adequate for a derivation of a point of departure. Although a few low risk-of-bias animal studies demonstrated selective histopathological changes in the kidney (such as proximal tubule injury, but without any significant changes in kidney dysfunction markers such as BUN or CRE), the studies were of insufficient duration (mostly sub-chronic), or small group size (less than 10 per sex per group), or considered inadequate to derive a point of departure for kidney dysfunction in humans. Overall, these studies were considered insufficient for derivation of a point of departure for kidney dysfunction in humans.

No point of departure was derived.

Sex hormone disruptions

In the human stream of evidence, 2 low-risk of bias cross-sectional studies were identified. While considered low risk of bias in the OHAT scoring, cross-sectional studies were not considered adequate for consideration in deriving a point of departure. Recent animal studies identified in the current review suggested an association with proxy measures of male infertility such as sperm quality and testicular damage; however, older multi-generational guideline rodent studies on reproductive toxicity indicated no association with number of pups delivered or with a fertility index. Weighing of evidence under Bradford Hill considerations was not strongly supportive of a causal association with fluoride in drinking water. Overall, these studies were considered insufficient for derivation of a point of departure for sex hormone derangement effects in humans.

No point of departure was derived.

8.4. Considerations for selection of most appropriate endpoint and a point of departure

The current review encompassed a thorough, multi-pronged examination of the effects of exposure to fluoride in drinking water on adverse health outcomes. The ultimate goal of this review was to provide evidence with which Health Canada could consider updating the current MAC for fluoride in drinking water. To identify the most sensitive and most appropriate endpoint of concern, the review included considerations for deriving an appropriate POD, for which there is good quality data demonstrating a well-defined exposure-response relationship. This examination involved the identification and assessment of quality of all new evidence from human, animal, and in vitro studies that had been published after the release of two CADTH reports in 2019 [2, 3], the NTP report in 2016 [413], and the Health Canada report in 2010 [1]. In synthesizing this evidence, the quality and potential risk of bias of individual studies was taken into consideration. The combined evidence generated from these different streams was then examined via the Bradford Hill considerations [414] for identification of credible causal adverse effects due to fluoride exposure.

In reconsidering an update of the MAC for fluoride in drinking water for North Americans, the HBV based on dental fluorosis was revisited using the newly published scientific evidence and

results from new modelling of the Dean (1942) data on dental fluorosis. Moderate dental fluorosis was selected as the level of fluorosis of concern by Health Canada. Furthermore, based on weight of evidence, four new endpoints were considered as credible candidates for most appropriate endpoint. While effects on sex hormones, thyroid dysfunction, and kidney dysfunction are potential adverse effects of fluoride exposure through drinking water, with enough supporting evidence to warrant concern, no points of departure were derived because of inadequate data sources to conduct dose-response modelling. The overall evidence identified to date strongly suggests that fluoride can affect cognitive outcomes in children (specifically, reduction in IQ scores), at levels close to those currently seen in North American drinking water.

Hence, the selection of the most appropriate endpoint requires a comparison of the point of departure for moderate dental fluorosis and the point of departure for IQ effects. For both endpoints, the vulnerable population is young, school-aged children, though critical periods of exposure likely differ (prenatal vs. early life).

First, the POD for moderate/ severe dental fluorosis was derived in the current report as:

- 1.56 mg/L for a BMR of 1%, 2.13 mg/L for a BMR of 5%, and 2.46 mg/L for a BMR of 10%

While data on moderate dental fluorosis could not be fit at the time of the US EPA report (2010) [406] using a classical approach, the current values were estimated using Bayesian model averaging to derive the extra risk-based BMDL across three alternative dose-response models using Bayesian BMD software, which only recently became available. The BMDL of 1.56 mg/L lies between the NOAEL of 1.3 mg/L and the LOAEL of 1.8 mg/L for moderate dental fluorosis in the Dean study.

Second, based on the weight of evidence to date, fluoride can credibly be considered to have an effect on childhood IQ. There is, however, significant uncertainty as to the POD. The draft NTP 2020 [103] and 2022 [104] reports concluded that evidence for effects below 1.5 mg/L was less consistent than that above 1.5 mg/L. Based on high quality MIREC and ELEMENT cohorts with individual-level measures, Grandjean and colleagues (2022) [399] estimated the benchmark concentration for maternal urinary fluoride associated with a 1-point reduction in IQ. Different linear and non-linear models fit by Grandjean and colleagues [399] resulted in benchmark

concentrations differing by more than 9-fold. Although the NRC concluded that fluoride is an endocrine disruptor, leading to thyroid dysfunction at very low exposure levels among individuals with iodine deficiency [415], the mechanism of action of fluoride for neurotoxicity is still poorly understood. Uncertainties in the shape of the dose-response curve at low levels of exposure to fluoride based on epidemiologic data will likely require extrapolation with a better understanding of the mechanism of action. For these reasons, a POD for IQ effects was provisionally selected as:

- 1.5 mg F/L, but acknowledging that credible support exists that the POD may be lower than this concentration (based on cohort data) and that the majority of studies to date are cross-sectional studies with significant concerns regarding exposure assessment and potential confounding.

Consideration should also be given to the severity of the two end points - moderate dental fluorosis and IQ reduction – for which PODs have been derived. The choice of a BMR of 1 IQ point (corresponding to a 1% reduction from a mean IQ of 100) has been adopted as an appropriate benchmark on this endpoint by several regulatory bodies, including the US EPA and EFSA. This level of cognitive effect (in the context of assessing the exposure to lead) has been shown to be associated with reduced educational attainment, employment status, productivity, and earned wages, reflecting substantial public health concerns [416].

Although outside of the scope of the present report, the establishment of an HBV for fluoride in drinking water will require consideration of possible adjustment factors to be applied to either of the two PODs derived above. Since the POD of 1.56 mg F/L for moderate dental fluorosis is based on high-quality population-based data in the target population (children), with only minor concern about other sources of ingested fluoride, a minimal adjustment factor could be entertained in deriving an HBV based on fluorosis. However, with currently available evidence suggesting that fluoride leads to reductions in children's IQ – arguably of more concern than moderate dental fluorosis – the possibility of cognitive effects in children should be taken into account in setting an HBV for fluoride in drinking water. As the POD for IQ reduction is not yet well defined, the POD of 1.56 mg F/L for moderate dental fluorosis may be preferred as a starting point for deriving the HBV. To allow for protection against potential cognitive effects in children at levels below the POD of 1.56 mg F/L, an additional overall database uncertainty factor could be applied to this POD.
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As additional information on the association between fluoride in drinking water and reduction in children's IQ becomes available, the choice of the most appropriate endpoint on which to base the POD to serve as the starting point to deriving an HBV for fluoride can be revisited.

A better understanding of low concentration fluoride risks

One of the challenges in evaluating the potential human health risks of fluoride is estimating risks at low levels of exposure. Following a comprehensive review of the scientific literature on health effects of fluoride in drinking water, neurological effects in children and dental fluorosis emerged as the two key endpoints with exposure-response data suitable for determination of a point of departure for risk assessment purposes. Dental fluorosis demonstrates a very steep exposure-response curve, with risk increasing markedly between 1 ppm F in drinking water, at which there is a low risk of mild dental fluorosis, and 4 ppm, where there is a high risk of severe dental fluorosis. Reductions in children's IQ – the key indicator of neurological impairment noted in human epidemiological studies – demonstrated a shallower exposure-response relationship, with less evidence of the threshold-like behavior seen for dental fluorosis.

Considering the currently available evidence, possible fluoride effects on childhood IQ should be taken into consideration as an area of public health concern, although less consistent evidence at low exposure levels remains a source of significant uncertainty. Benchmark dose modeling of high-quality epidemiologic data by Grandjean et al. 2022 [399] predicted increased risks at levels lower than 1 mg/L F in drinking water; however, different models – including linear, quadratic, and segmented models – predicted notably different levels of risk from fluoride at these low concentrations. At this point in time, mechanistic explanation and key mode of action events are insufficiently understood to guide the choice of the most appropriate model to use for predicting risks at low exposure levels.

Given the challenges of using available epidemiological data to characterize potential fluoride health effects at low levels of exposure with a high degree of precision, an evaluation of the biological mode and mechanisms of action underlying fluoride toxicity was included in the current review to provide some guidance on extrapolation at low concentrations. Although fluoride was found to cause a number of biological changes through various toxicity pathways (including oxidative stress, changes in gene expression, mitochondrial dysfunction, ER stress,

perturbation of the Na/K+ ATPase pathway, apoptosis, inflammation, or death receptor-mediated pathways), the evidence from in vitro studies was considered to be too non-specific for health endpoints to, in particular, explain the occurrence of neurological effects in children following fluoride exposure. Absent a clear understanding of the underlying biological mechanisms and mode of action by which exposure to fluoride may act to reduce children's IQ, evidence for such effects below 1.5 mg/L remains uncertain. Experimental studies are needed to better understand the key mode of action events and their timing with respect to neurodevelopmental effects following maternal and early life exposure to fluoride [394]. Future epidemiologic studies incorporating molecular and genetic components may also be of value in clarifying the shape of the exposure-response curve at low concentrations.

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