



SUPPLEMENTARY MATERIAL

Critical Review of Potential Adverse Health Effects of Fluoride in Drinking Water

Prepared for:
Health Canada

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Section 1. Literature search for human and animal Studies

Strategy

Search Question	Are there any health risks to exposure to fluoride in water?		
Major Concept s	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, fluoride, 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

Summary of output

Searched databases	Publications	Level of selection of publications
Medline	295	3 concepts (2016-current)
EMBASE	591	3 concepts (2016-current)
PubMed	214	3 concepts (2016-current)
CINAHL	18	3 concepts (2016-current)
Toxline	215	3 concepts (2016-current)
PAIS index	178	Fl + water
Health Technology Assessment	3	Fl + water

Cochrane Library (Willey)	0	FI + water
Cochrane Database of Systematic Reviews	28	FI + water (2016-current)
Cochrane Central Register of Controlled Trials	34	FI + water (2016-current)
Trials, WHO	104	FI (completed, with results)
Trials, EU	7	FI (completed, with results)
Trials, ISRCTN	18	FI (completed, with results)
Trials, USA	161	FI (completed, with results)
Trials, UK	0	FI (all)
Trials, Canada	10	FI (all)
Grey Literature (18 databases)	339	
Background	18	
TOTAL – before deduplication	2,233	
TOTAL – after deduplication	1,639	

Bibliographic database search terms and output

Medline Ovid ¹

Concept	#	Medline query	Results
Fluoride	1	exp Fluorides/	36,671
	2	exp Fluoridation/	5,807
	3	fluorid*.tw.	46,815
	4	fluorin*.tw.	24,699
	5	flurin*.tw.	6
	6	flurid*.tw.	232
	7	or/1-6	83,947
Water	8	Water/	153,755
	9	water.tw.	748,212
	10	Drinking Water/	7,719

¹ 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	Results
	11	drinking water.tw.	47,159
	12	exp Fresh Water/	62,271
	13	fresh water*.tw.	6,372
	14	freshwater*.tw.	34,209
	15	exp Mineral Waters/	4,263
	16	mineral water*.tw.	3,217
	17	exp Carbonated Water/	55
	18	carbonated water*.tw.	140
	19	exp Water Quality/	5,886
	20	(water adj3 quality).tw.	21,935
	21	exp Water Resources/	779
	22	(water* adj3 resource*).tw.	5,689
	23	Water Supply/	32,288
	24	(water adj3 supply).tw.	8,648
	25	(water* adj3 course*).tw.	524
	26	watercourse*.tw.	617
	27	exp Rivers/	25,532
	28	river*.tw.	61,402
	29	exp Lakes/	8,576
	30	lake*.tw.	37,378
	31	exp Ponds/	1,384
	32	pond*.tw.	16,113
	33	exp Groundwater/	9,100
	34	groundwater*.tw.	18,480
	35	ground water*.tw.	3,463
	36	Water Wells/	703
	37	water well*.tw.	501
	38	(water* adj3 course*).tw.	524
	39	watercourse*.tw.	617

Concept	#	Medline query	Results
	40	exp Natural Springs/	2,026
	41	natural spring*.tw.	101
	42	exp Hot Springs/	1,851
	43	hot spring*.tw.	2,056
	44	hotspring*.tw.	21
	45	spring water*.tw.	939
	46	springwater*.tw.	22
	47	(water* adj3 reservoir*).tw.	3,162
	48	stream*.tw.	65,949
	49	brook*.tw.	6,086
	50	creek*.tw.	3,148
	51	rivulet*.tw.	83
	52	rill*.tw.	120
	53	runnel*.tw.	23
	54	community water.tw.	523
	55	water fluoridation.tw.	1,267
	56	community water fluoridation.tw.	204
	57	CWF.tw.	121
	58	or/8-57	957,393
Outcomes	59	exp Fluoride Poisoning/	1,046
	60	(fluoride adj3 poisoning).tw.	121
	61	exp Bone Diseases/	492,641
	62	cancer*.tw.	1,705,562
	63	exp Neoplasms/	3,270,255
	64	neoplas*.tw.	255,862
	65	malignan*.tw.	556,683
	66	tumor*.tw.	1,397,806
	67	tumour*.tw.	264,641
	68	sarcoma*.tw.	93,670

Concept	#	Medline query	Results
	69	carcinoma*.tw.	641,006
	70	tumor*.tw.	1,397,806
	71	(bone* adj3 disease*).tw.	24,734
	72	exp Bone Development/	60,998
	73	(bone* adj3 develop*).tw.	13,828
	74	exp Fractures, Bone/	180,742
	75	(bone* adj3 fracture*).tw.	20,569
	76	(bone* adj3 injur*).tw.	3,795
	77	(skelet* adj3 fluorosis).tw.	395
	78	(skelet* adj3 toxicit*).tw.	226
	79	exp Bone Neoplasms/	124,454
	80	(bone* adj3 cancer*).tw.	8,270
	81	(bone* adj3 neoplasm*).tw.	1,101
	82	(bone* adj3 tumor*).tw.	15,408
	83	(bone* adj3 tumour*).tw.	3,350
	84	(skelet* adj3 cancer*).tw.	680
	85	(skelet* adj3 neoplasm*).tw.	156
	86	(skelet* adj3 tumor*).tw.	1,057
	87	(skelet* adj3 tumour*).tw.	224
	88	exp Endocrine System Diseases/	963,395
	89	(endocrin* adj3 diseas*).tw.	5,078
	90	(endocrin* adj3 disorder*).tw.	6,324
	91	(endocrin* adj3 disturbance*).tw.	1,103
	92	(endocrin* adj3 disruption*).tw.	2,393
	93	(endocrin* adj3 dysfunction*).tw.	1,913
	94	endocrinopath*.tw.	3,522
	95	(hormon* adj3 disease*).tw.	3,312
	96	(hormon* adj3 disorder*).tw.	1,860
	97	(hormon* adj3 disruption*).tw.	506

Concept	#	Medline query	Results
	98	(hormon* adj3 dysfunction*).tw.	893
	99	(hormon* adj3 imbalance*).tw.	1,285
	100	exp Thyroid Diseases/	145,756
	101	(thyroid* adj3 diseas*).tw.	18,323
	102	(thyroid* adj3 disorder*).tw.	4,827
	103	(thyroid* adj3 dysfunction*).tw.	5,515
	104	(thyroid* adj3 abnormalit*).tw.	1,697
	105	(thyroid* adj3 anomal*).tw.	171
	106	Neurodevelopmental Disorders/	1,867
	107	(neurodevelopment* adj3 disorder*).tw.	9,811
	108	(neurodevelopment* adj3 diseas*).tw.	936
	109	exp Developmental Disabilities/	19,663
	110	(development* adj3 disabilit*).tw.	7,213
	111	(development* adj3 dela*).tw.	25,513
	112	(development* adj3 abnormalit*).tw.	7,736
	113	Intellectual Disability/	54,031
	114	(intellectual adj3 disabilit*).tw.	17,201
	115	(intellectual adj3 dysfunction*).tw.	156
	116	(intellectual adj3 impairment*).tw.	1,880
	117	exp Neurocognitive Disorders/	247,000
	118	neurocognitive disorder*.tw.	2,171
	119	exp cognition disorders/	90,921
	120	(cogniti* adj3 disorder*).tw.	9,248
	121	(cogniti* adj3 disease*).tw.	6,696
	122	exp Cognitive Dysfunction/	15,133
	123	(cogniti* adj3 dysfunction*).tw.	16,461
	124	Immune System Diseases/	12,177
	125	immunotoxic*.tw.	3,937
	126	immunopath*.tw.	16,870

Concept	#	Medline query	Results
	127	(immun* adj3 disease*).tw.	47,361
	128	(immun* adj3 disorder*).tw.	14,597
	129	(immun* adj3 dysfunction*).tw.	7,378
	130	(immun* adj3 dysregulation*).tw.	4,671
	131	Hypersensitivity/	48,076
	132	Hypersensitivity, Delayed/	18,978
	133	Hypersensitivity, Immediate/	12,492
	134	hypersensitivit*.tw.	60,456
	135	genotoxic*.tw.	32,443
	136	exp male urogenital diseases/	1,108,660
	137	exp Female Urogenital Diseases/	1,224,494
	138	(urogen* adj3 disease*).tw.	602
	139	(urogen* adj3 disorder*).tw.	211
	140	(genitourinary adj3 disease*).tw.	617
	141	(genitourinary adj3 disorder*).tw.	233
	142	(male adj3 genit*).tw.	5,723
	143	(female adj3 genit*).tw.	12,463
	144	(health adj3 hazard*).tw.	11,187
	145	(health adj3 risk*).tw.	56,982
	146	or/59-145	6,674,313
Fluoride + water	147	7 and 58	12,883
Fluoride + water + outcomes	148	7 and 58 and 146	1,372
2016 - current	149	limit 148 to yr="2016 -Current"	295
Reviews only	150	limit 149 to (meta analysis or "review" or "scientific integrity review" or "systematic review" or	28

Concept	#	Medline query	Results
		systematic reviews as topic)	

EMBASE ²

Concept	#	EMBASE query	Results
Fluoride	1	exp fluoride/	35,562
	2	exp fluoridation/	6,256
	3	fluorid*.tw.	55,488
	4	fluorin*.tw.	29,336
	5	flurin*.tw.	21
	6	flurid*.tw.	209
	7	or/1-6	91,990
Water	8	water/	317,883
	9	water.tw.	949,249
	10	drinking water/	51,062
	11	drinking water.tw.	65,801
	12	exp tap water/	8,446
	13	tap water.tw.	13,667
	14	tapwater.tw.	240
	15	exp fresh water/	23,207
	16	fresh water*.tw.	8,517
	17	freshwater*.tw.	37,613
	18	water quality/	41,343
	19	water quality.tw.	27,273
	20	water treatment/	19,840
	21	water treatment.tw.	15,241
	22	exp water supply/	40,847
	23	(water adj3 supply*).tw.	12,420
	24	(water* adj3 resource*).tw.	7,716
	25	(water* adj3 reservoir*).tw.	4,029
	26	(water* adj3 course*).tw.	836
	27	watercourse*.tw.	935

² Embase: Excerpta Medica Database Guide

Concept	#	EMBASE query	Results
	28	exp river/	30,610
	29	river*.tw.	78,325
	30	exp lake/	15,700
	31	lake*.tw.	47,036
	32	exp pond/	4,829
	33	pond*.tw.	20,683
	34	exp ground water/	26,252
	35	ground water*.tw.	6,199
	36	groundwater*.tw.	24,734
	37	exp well water/	2,975
	38	(water adj3 well*).tw.	11,793
	39	exp mineral water/	5,338
	40	mineral water*.tw.	3,986
	41	exp carbonated water/	130
	42	carbonated water*.tw.	191
	43	exp natural spring/	242
	44	natural spring*.tw.	143
	45	exp thermal spring/	2,971
	46	hot spring*.tw.	2,377
	47	hotspring*.tw.	31
	48	spring water*.tw.	1,353
	49	springwater*.tw.	34
	50	exp "stream (river)"/	4,325
	51	stream*.tw.	94,825
	52	brook*.tw.	8,456
	53	creek*.tw.	3,927
	54	rivulet*.tw.	90
	55	rill*.tw.	232
	56	runnel*.tw.	32
	57	community water.tw.	646

Concept	#	EMBASE query	Results
	58	water fluoridation.tw.	1,412
	59	or/8-58	1,221,777
Outcomes	60	exp fluorosis/	3,316
	61	fluoride intoxication.tw.	193
	62	fluoride poisoning.tw.	173
	63	fluoridosis.tw.	1
	64	exp neoplasm/	4,779,286
	65	exp malignant neoplasm/	3,584,172
	66	neoplas*.tw.	367,025
	67	cancer*.tw.	2,481,147
	68	malignan*.tw.	834,120
	69	carcinoma*.tw.	912,502
	70	sarcoma*.tw.	132,200
	71	tumor*.tw.	1,962,716
	72	tumour*.tw.	426,488
	73	exp bone disease/	1,204,429
	74	(bone* adj3 diseas*).tw.	37,645
	75	(bone* adj3 disorder*).tw.	9,155
	76	(skelet* adj3 disease*).tw.	5,669
	77	(skelet* adj3 disorder*).tw.	4,132
	78	exp bone injury/	324,785
	79	(bone* adj3 injur*).tw.	5,259
	80	(bone* adj3 damage*).tw.	5,463
	81	(bone* adj3 fracture*).tw.	29,849
	82	(bone* adj3 trauma).tw.	1,545
	83	(skelet* adj3 injur*).tw.	3,537
	84	(skelet* adj3 damage*).tw.	1,753
	85	(skelet* adj3 fracture*).tw.	1,880
	86	(skelet* adj3 trauma).tw.	781
	87	exp bone development/	111,099

Concept	#	EMBASE query	Results
	88	(bone* adj3 develop*).tw.	19,862
	89	osteogenesis.tw.	25,397
	90	(skelet* adj3 develop*).tw.	10,605
	91	skeletogenesis.tw.	963
	92	exp bone cancer/	101,542
	93	(bone* adj3 cancer*).tw.	12,509
	94	(bone* adj3 tumor*).tw.	21,086
	95	(bone* adj3 tumour*).tw.	5,398
	96	(bone* adj3 neoplasm*).tw.	1,538
	97	osteosarcoma*.tw.	29,630
	98	(skelet* adj3 cancer*).tw.	1,014
	99	(skelet* adj3 tumor*).tw.	1,422
	100	(skelet* adj3 tumour*).tw.	378
	101	(skelet* adj3 neoplasm*).tw.	205
	102	exp endocrine disease/	2,152,614
	103	(endocrin* adj3 disease*).tw.	7,901
	104	(endocrin* adj3 disorder*).tw.	10,179
	105	(endocrin* adj3 disturbance*).tw.	2,684
	106	(endocrin* adj3 dysfunction*).tw.	3,058
	107	(endocrin* adj3 disruption*).tw.	2,901
	108	endocrinopath*.tw.	5,698
	109	(hormon* adj3 disorder*).tw.	2,821
	110	(hormon* adj3 disruption*).tw.	609
	111	(hormon* adj3 dysfunction*).tw.	1,433
	112	(hormon* adj3 imbalance*).tw.	2,125
	113	thyroid disease/	31,956
	114	(thyroid* adj3 disease*).tw.	27,151
	115	(thyroid* adj3 disorder*).tw.	7,659
	116	(thyroid* adj3 abnormalit*).tw.	2,621
	117	(thyroid* adj3 anomal*).tw.	262

Concept	#	EMBASE query	Results
	118	(thyroid* adj3 dysfunction*).tw.	8,785
	119	exp mental disease/	2,280,520
	120	(mental adj3 disease*).tw.	8,547
	121	(mental adj3 disorder*).tw.	58,262
	122	(mental adj3 disturbance*).tw.	3,494
	123	(mental adj3 illness*).tw.	41,522
	124	(neurodevelopment* adj3 disorder*).tw.	13,066
	125	(neuropsychiatric adj3 disorder*).tw.	13,872
	126	(psych* adj3 disease*).tw.	21,908
	127	(psych* adj3 disorder*).tw.	103,146
	128	(psych* adj3 disturbance*).tw.	10,811
	129	(psych* adj3 illness*).tw.	22,244
	130	exp developmental disorder/	44,227
	131	(development* adj3 disorder*).tw.	31,349
	132	(development* adj3 disease*).tw.	69,819
	133	(development* adj3 disabilit*).tw.	9,938
	134	(development* adj3 dela*).tw.	36,568
	135	(development* adj3 abnormalit*).tw.	10,461
	136	exp intellectual impairment/	528,459
	137	(intellectual adj3 impairment*).tw.	2,773
	138	(intellectual adj3 disabilit*).tw.	25,169
	139	(intellectual adj3 dysfunction*).tw.	196
	140	exp cognitive defect/	485,131
	141	(cogniti* adj3 defect*).tw.	1,217
	142	(cogniti* adj3 disorder*).tw.	14,749
	143	(cogniti* adj3 deficit*).tw.	37,950
	144	(cogniti* adj3 disabilit*).tw.	4,447
	145	(cogniti* adj3 impairment*).tw.	104,619
	146	(cogniti* adj3 dysfunction*).tw.	25,318
	147	exp immunopathology/	1,861,146

Concept	#	EMBASE query	Results
	148	immunopath*.tw.	21,949
	149	(immun* adj3 disease*).tw.	66,959
	150	(immun* adj3 disorder*).tw.	21,255
	151	(immun* adj3 dysfunction*).tw.	10,633
	152	(immun* adj3 dysregulation*).tw.	7,542
	153	exp hypersensitivity/	667,780
	154	hypersensitivit*.tw.	86,607
	155	exp genotoxicity/	32,891
	156	genotoxic*.tw.	40,197
	157	exp urogenital tract disease/	2,543,465
	158	(urogenital adj3 disease*).tw.	861
	159	(urogenital adj3 disorder*).tw.	340
	160	(genitourinary adj3 disease*).tw.	868
	161	(genitourinary adj3 disorder*).tw.	311
	162	(male adj3 genit*).tw.	6,960
	163	(female adj3 genit*).tw.	16,842
	164	exp health hazard/	551,767
	165	(health adj3 hazard*).tw.	14,826
	166	(health adj3 risk*).tw.	70,092
	167	or/60-166	12,825,673
Fluoride + water	168	7 and 59	16,549
Fluoride + water + outcomes	169	7 and 59 and 167	3,175
2016 - current	170	limit 169 to yr="2016 -Current"	591
Reviews only	171		52

PubMed

Concept	#	Pubmed Query	Results
Fluoride	1	fluoride[MeSH Terms]	36,648
	2	fluoridation[MeSH Terms]	5,806
	3	fluorid*[Text Word]	62,000
	4	fluorin*[Text Word]	38,116
	5	flurin*[Text Word]	6
	6	flurid*[Text Word]	248
	7	(((((fluoride[MeSH Terms]) OR fluoridation[MeSH Terms]) OR fluorid*[Text Word]) OR fluorin*[Text Word]) OR flurin*[Text Word] OR flurid*[Text Word]))	97,663
Water	8	water[MeSH Terms]	172,538
	9	water[Text Word]	929,227
	10	drinking water[MeSH Terms]	7,746
	11	drinking water[Text Word]	49,377
	12	tap water[MeSH Terms]	2,551
	13	tap water[Text Word]	10,337
	14	fresh water[MeSH Terms]	62,169
	15	fresh water*[Text Word]	34,531
	16	freshwater*[Text Word]	34,861
	17	water quality[MeSH Terms]	5,869
	18	water qualit*[Text Word]	21,220
	19	water treatment[MeSH Terms]	31,226
	20	water treatment*[Text Word]	10,810
	21	water supply[MeSH Terms]	32,795
	22	water supply[Text Word]	36,524
	23	water resource[MeSH Terms]	767
	24	water resource*[Text Word]	5,510
	25	water reservoir*[Text Word]	1,443
	26	water course[Text Word]	61

Concept	#	Pubmed Query	Results
	27	watercourse*[Text Word]	618
	28	river[MeSH Terms]	25,486
	29	river*[Text Word]	67,451
	30	lake[MeSH Terms]	8,549
	31	lake*[Text Word]	38,201
	32	pond[MeSH Terms]	1,379
	33	pond*[Text Word]	16,095
	34	ground water[MeSH Terms]	9,078
	35	ground water*[Text Word]	3,472
	36	groundwater*[Text Word]	20,109
	37	water well[MeSH Terms]	700
	38	water well*[Text Word]	1,061
	39	mineral water[MeSH Terms]	4,261
	40	mineral water*[Text Word]	5,495
	41	carbonated water[MeSH Terms]	55
	42	carbonated water*[Text Word]	168
	43	natural spring[MeSH Terms]	2,024
	44	natural spring*[Text Word]	263
	45	thermal spring*[Text Word]	302
	46	hot spring[MeSH Terms]	1,850
	47	hot spring*[Text Word]	2,520
	48	hotspring*[Text Word]	21
	49	spring water[MeSH Terms]	1,637
	50	spring water*[Text Word]	926
	51	springwater*[Text Word]	23
	52	stream[MeSH Terms]	25,486
	53	stream*[Text Word]	66,641
	54	brook*[Text Word]	6,169
	55	creek*[Text Word]	3,168

Concept	#	Pubmed Query	Results
		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	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	5,037,262

Concept	#	Pubmed Query	Results
		<p>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, amnesic, 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</p>	

Concept	#	Pubmed Query	Results
		<p>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* 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*</p>	

Concept	#	Pubmed Query	Results
		<p>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 cognit* impair*[Text Word]) OR cognit* disease*[Text Word]) OR cognit* defect*[Text Word]) OR cognit* deficit*[Text Word]) OR cognit* disabilit*[Text Word]) OR cognit* 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</p>	

Concept	#	Pubmed Query	Results
		<p>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 cognit* impair*[Text Word]) OR cognit* disease*[Text Word]) OR cognit* defect*[Text Word]) OR cognit* deficit*[Text Word]) OR cognit* disabilit*[Text Word]) OR cognit* 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 hypersensitiv*[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])</p>	
	69	Limit 68 to (meta analysis or "review" or "scientific integrity review" or "systematic review" or systematic reviews as topic)	19

CINAHL ³

Concept	#	Cinahl query	Results
Fluoride	1	fluoride	5,449
	2	fluoride in water	1,142

³ Cumulative Index to Nursing and Allied Health Literature

Concept	#	Cinahl query	Results	
Water	3	water fluoridation or fluoridation of water or fluoride treatment or fluoride in water	1,552	
	4	fluoridation or fluoride or fluoridated	6,246	
	5	TX water fluorid* OR TX fluorid* OR TX fluorin* OR TX flurin* OR TX flurid*	8,118	
	6	S1 OR S2 OR S3 OR S4 OR S5	8,118	
	7	drinking water OR tap water	112	
	8	TX drinking water OR TX tap water	26	
	9	drinking water quality OR drinking water treatment OR drinking water safety	11,746	
	10	TX drinking water quality OR TX drinking water treatment OR TX drinking water safety	711	
	11	ground water OR water wells OR river OR lake OR pond	6,317	
	12	TX ground water OR TX water wells OR TX river OR TX lake OR TX pond	49,341	
	13	mineral water OR carbonated water OR spring water OR hot springs	645	
	14	TX mineral water OR TX carbonated water OR TX spring water OR TX hot springs	991	
	15	S7 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	50,317	
	Outcomes	16	fluorosis	687
		17	fluoride toxicity	28
18		bone disease	11,078	
19		TX bone* disease*	12,465	
20		bone disorder	1,335	
21		TX bone* disorder*	1,576	
22		skeletal disease	757	
23		TX skelet* disease*	954	
24		skeletal disorders	542	
25		TX skelet* disorder*	641	

Concept	#	Cinahl query	Results
	26	bone injury	4,342
	27	TX bone* injur*	4,225
	28	bone fracture	6,903
	29	TX bone* fracture*	7,351
	30	TX bone* damage*	788
	31	bone trauma	615
	32	TX bone* trauma*	1,049
	33	TX skelet* injur*	1,799
	34	TX skelet* damage*	241
	35	TX skelet* fracture*	621
	36	skeletal trauma	173
	37	TX skelet* trauma*	319
	38	bone development	2,675
	39	TX bone* development*	3,347
	40	osteogenesis	5,604
	41	TX osteogen*	6,675
	42	TX skelet* develop*	931
	43	TX skeletogen*	22
	44	bone cancer	8,333
	45	TX bone* cancer*	3,117
	46	bone tumor	10,075
	47	TX bone* tumor*	3,054
	48	TX bone* tumour*	768
	49	bone neoplasm	10,075
	50	TX bone* neoplas*	8,269
	51	osteosarcoma	3,482
	52	TX osteosarcoma*	3,505
	53	osteogenic sarcoma	2,222
	54	TX osteogenic sarcoma*	103
	55	TX skelet* cancer*	358

Concept	#	Cinahl query	Results
	56	TX skelet* tumor*	251
	57	TX skelet* tumour*	57
	58	TX skelet* neoplas*	35
	59	endocrine disease	1,971
	60	TX endocrin* disease*	4,212
	61	endocrine disorders	1,526
	62	TX endocrin* disorder*	2,260
	63	endocrine disruptors	312
	64	endocrine disrupting chemicals	310
	65	TX endocrin* disrupt*	953
	66	TX endocrin* disturbance*	121
	67	TX endocrin* dysfunction*	315
	68	endocrine pathology	232
	69	TX endocrin* patholo*	391
	70	TX endocrinopath*	465
	71	TX hormon* disease*	1,380
	72	hormone disorders	252
	73	TX hormon* disorder*	544
	74	hormone disruptor	13
	75	TX hormon* disruptor*	28
	76	hormone imbalance	68
	77	TX hormon* imbalance*	204
	78	TX hormon* dysfunction*	269
	79	thyroid disease	4,066
	80	TX thyroid* disease*	4,324
	81	thyroid disorders	2,129
	82	TX thyroid* disorder*	773
	83	thyroid cancer	6,329
	84	TX thyroid* cancer*	4,093
	85	thyroid neoplasms	6,018

Concept	#	Cinahl query	Results
	86	TX thyroid* neoplas*	5,768
	87	thyroid adenoma	4,888
	88	TX thyroid* adenoma*	213
	89	TX thyroid* abnormalit*	363
	90	TX thyroid* anomal*	34
	91	thyroid dysfunction	861
	92	TX thyroid* dysfunction*	894
	93	water fluoridation cancer	7
	94	mental disease	74,025
	95	TX mental* disease*	5,581
	96	mental disorders	74,025
	97	TX mental* disorder*	69,886
	98	mental illness	74,025
	99	TX mental* illness*	24,630
	100	mental disabilities	52,583
	101	TX mental* disabilit*	4,376
	102	mental disturbance	392
	103	TX mental* disturbance*	413
	104	psychiatric disease	4,405
	105	TX psych* disease*	23,501
	106	psychiatric disorders	46,279
	107	TX psych* disorder*	78,576
	108	psychiatric illness	4,405
	109	TX psych* illness*	12,623
	110	TX psych* disturbance*	1,590
	111	TX deveopment* disease*	1
	112	developmental disorders	4,344
	113	TX development* disorder*	18,045
	114	developmental disabilities	11,039
	115	TX development* disabilit*	23,179

Concept	#	Cinahl query	Results
	116	developmental delay	3,211
	117	TX development* dela*	5,733
	118	TX development* abnormalit*	1,109
	119	intellectual disability	21,791
	120	TX intellectual disabilit*	25,228
	121	intellectual impairment	551
	122	TX intellectual impairment*	587
	123	TX intellectual dysfunction*	46
	124	cognitive disease	6,663
	125	TX cogniti* disease*	6,958
	126	cognitive disorders	22,546
	127	TX cogniti* disorder*	33,291
	128	TX cogniti* defect*	128
	129	cognitive deficits	23,070
	130	TX cogniti* deficit*	6,535
	131	cognitive disabilities	1,853
	132	TX cogniti* disabilit*	2,223
	133	cognitive impairment	33,788
	134	TX cogniti* impairment*	24,208
	135	cognitive dysfunction	21,313
	136	TX cogniti* dysfunction*	4,332
	137	TX cogniti* dysregulation*	133
	138	immune disease	3,588
	139	TX immun* disease*	24,209
	140	immune disorders	1,547
	141	TX immun* disorder*	3,161
	142	immune dysfunction	784
	143	TX immun* dysfunction*	1,343
	144	immune dysregulation	671
	145	TX immun* dysregulation*	765

Concept	#	Cinahl query	Results
	146	immunopathogenesis	410
	147	TX immunopath*	1,626
	148	hypersensitivity	23,866
	149	TX hypersensitiv*	24,399
	150	genotoxicity	597
	151	genotoxic	759
	152	TX genotoxic*	1,150
	153	TX urogenital disease*	893
	154	urogenital disorder	31
	155	TX urogenital disorder*	32
	156	urogenital dysfunction	27
	157	TX urogenital dysfunction*	29
	158	TX genitourinary disease*	224
	159	TX genitourinary disorder*	89
	160	TX genitourinary dysfunction	32
	161	male genitalia	2,351
	162	TX male* genit*	2,315
	163	female genitalia	7,135
	164	TX female* genit*	7,079
	165	health hazards	2,380
	166	TX health hazard*	4,258
	167	health risks	34,021
	168	TX health risk*	40,954
	169	cancer	389,786
	170	TX cancer*	499,978
	171	neoplasm	486,986
	172	TX neoplas*	426,880
	173	malignancy	82,898
	174	malignant	35,357
	175	TX malignan*	64,192

Concept	#	Cinahl query	Results
	176	tumor	486,986
	177	TX tumor*	162,815
	178	tumour	486,986
	179	TX tumour*	26,499
	180	carcinoma	93,540
	181	TX carcino*	105,458
	182	sarcoma	11,749
	183	TX sarcoma*	13,020
	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	1,088,674

Concept	#	Cinahl query	Results
		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 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	1,736,713
	186	S6 AND S15	168
	187	S6 AND S15 AND S184	87
	188	S6 AND S15 AND S184 AND S185	18

Toxnet ⁴

Concept	#	Query	Results
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]))	97,663
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 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	1,042,045

⁴ The toxicology literature database for the National Institutes of Health, USA

Concept	# Query	Results
	<p>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 Word]) OR immunologic* dysfunction*[Text Word]) OR immunologic* dysregulat*[Text Word]) OR immediate</p>	

Concept	#	Query	Results
		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]))))	
Toxicology	4	tox [subset]	5,639,829
Fl + water	5	1 AND 2	14,344
Fl + water	6	1 AND 2 AND 3	1,400
		+ outcomes	
Fl + water	7	1 AND 2 AND 3 AND 4	940
		+ outcomes (toxicology)	
2016- current		limit 7 to yr="2016 -Current"	215

PAIS Index

Concept	#	PAIS query	Results
Fluoride	1	su(fluoride) OR su(Fluorides) OR su(fluoridation) OR su(fluoridation of water) OR su(fluoridation of drinking water)	223
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)	26,939
	3	su(Ground Water) OR su(water wells) OR su(Rivers) OR su(Lakes) OR su(Ponds) OR su(Water Sources)	7,094
	4	su(mineral water) OR su(carbonated water) OR su(spring water) OR su(Hot Springs)	223
	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))	30,512
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	179

Concept	#	PAIS query	Results
		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	Results
Fluoride	1	exp Fluorides/	4
	2	exp Fluoridation/	2
	3	fluorid*.tw.	11
	4	fluorin*.tw.	1
	5	flurin*.tw.	0
	6	flurid*.tw.	0
	7	or/1-6	12
Water	8	exp Water/	6

9	drinking water.tw.	1
10	tap water*.tw.	3
11	exp water supply/	4
12	(water* adj3 suppl*).tw.	3
13	(water* adj3 treatment*).tw.	1
14	exp Water Purification/	1
15	(water* adj3 purification).tw.	1
16	lake*.tw.	7
17	pond*.tw.	1
18	ground water*.tw.	0
19	exp mineral waters/	1
20	mineral water*.tw.	1
21	hot spring*.tw.	1
22	communit* water*.tw.	0
23	or/8-22	24

Fluoride +	24	7 and 23	3
water			

Concept	#	CDSR query	Results
Fluoride	1	fluoride.mp. [mp=title, abstract, full text, keywords, caption text]	87
	2	fluoridation.mp. [mp=title, abstract, full text, keywords, caption text]	19
	3	fluorin*.mp. [mp=title, abstract, full text, keywords, caption text]	19
	4	flurin*.mp. [mp=title, abstract, full text, keywords, caption text]	2
	5	flurid*.mp. [mp=title, abstract, full text, keywords, caption text]	2
	6	or/1-5	107
Water	7	water.mp. [mp=title, abstract, full text, keywords, caption text]	1,236
	8	drinking water.mp. [mp=title, abstract, full text, keywords, caption text]	53
	9	tap water.mp. [mp=title, abstract, full text, keywords, caption text]	34
	10	(water adj3 fluorid*).mp. [mp=title, abstract, full text, keywords, caption text]	21
	11	community water*.mp. [mp=title, abstract, full text, keywords, caption text]	4
	12	fresh water.mp. [mp=title, abstract, full text, keywords, caption text]	8
	13	freshwater.mp. [mp=title, abstract, full text, keywords, caption text]	11
	14	ground water.mp. [mp=title, abstract, full text, keywords, caption text]	3
	15	groundwater.mp. [mp=title, abstract, full text, keywords, caption text]	3

Concept	#	CDSR query	Results
	16	(water* adj3 well*).mp. [mp=title, abstract, full text, keywords, caption text]	25
	17	mineral water*.mp. [mp=title, abstract, full text, keywords, caption text]	12
	18	carbonated water*.mp. [mp=title, abstract, full text, keywords, caption text]	2
	19	spring water*.mp. [mp=title, abstract, full text, keywords, caption text]	1
	20	(water* adj3 resource*).mp. [mp=title, abstract, full text, keywords, caption text]	4
	21	(water* adj3 source*).mp. [mp=title, abstract, full text, keywords, caption text]	31
	22	(water* adj3 suppl*).mp. [mp=title, abstract, full text, keywords, caption text]	60
	23	river*.mp. [mp=title, abstract, full text, keywords, caption text]	222
	24	lake*.mp. [mp=title, abstract, full text, keywords, caption text]	87
	25	pond*.mp. [mp=title, abstract, full text, keywords, caption text]	72
	26	or/7-25	1,535
Fluoride + water	27	6 and 26	46
2016 - current	28	limit 27 to last 5 years	28

Cochrane Central Register of Controlled Trials (CENTRAL)

Concept	#	CENTRAL query	Results
Fluoride	1	exp fluorides/	2,477
	2	exp Fluoridation/	35

Concept	#	CENTRAL query	Results
	3	fluorid*.tw.	4,442
	4	fluorin*.tw.	322
	5	flurin*.tw.	1
	6	flurid*.tw.	8
	7	or/1-6	5,265
Water	8	water/	1,909
	9	exp Drinking Water/	116
	10	drinking water.tw.	756
	11	tap water.tw.	528
	12	tapwater.tw.	5
	13	exp Water Quality/	34
	14	(water adj3 quality).tw.	256
	15	community water.tw.	12
	16	water fluoridation.tw.	17
	17	exp groundwater/	17
	18	groundwater*.tw.	38
	19	ground water*.tw.	10
	20	exp Water Wells/	5
	21	(water* adj3 well*).tw.	238
	22	exp Natural Springs/	10
	23	natural spring*.tw.	7
	24	hot spring*.tw.	29
	25	springwater.tw.	2
	26	spring water*.tw.	46
	27	exp Mineral Waters/	127
	28	minteral water*.tw.	-
	29	exp Carbonated Water/	6
	30	carbonated water*.tw.	43
	31	exp fresh water/	31
	32	fresh water*.tw.	42

Concept	#	CENTRAL query	Results
	33	freshwater*.tw.	47
	34	exp Lakes/	4
	35	lake*.tw.	717
	36	exp Ponds/	-
	37	pond*.tw.	262
	38	exp Rivers/	4
	39	river*.tw.	737
	40	exp water supply/	166
	41	(water* adj3 suppl*).tw.	399
	42	or/8-41	5,743
Fluoride + water	43	7 and 42	191
2016 - current	44	limit 43 to yr="2016 -Current"	34

Cochrane Library (Wiley)

Concept	#	Cochrane query	Results
	1	MeSH descriptor: [Fluorides] in all MeSH products	2489
	2	MeSH descriptor: [Fluoridation] explode all trees	38
	3	(fluorid*):ti,ab,kw	4917
	4	#1 OR #2 OR #3	5001
	5	MeSH descriptor: [Drinking Water] explode all trees	125
	6	MeSH descriptor: [Water Quality] explode all trees	35
	7	#5 OR #6	144
	8	MeSH descriptor: [Bone Development] explode all trees	748
	9	MeSH descriptor: [Bone Diseases] explode all trees	12566
	10	MeSH descriptor: [Fractures, Bone] explode all trees	5600
	11	MeSH descriptor: [Bone Neoplasms] explode all trees	1195
	12	MeSH descriptor: [Osteosarcoma] explode all trees	250
	13	MeSH descriptor: [Endocrine System Diseases] explode all trees	38563
	14	MeSH descriptor: [Endocrine Disruptors] explode all trees	8

Concept	#	Cochrane query	Results
	15	MeSH descriptor: [Thyroid Diseases] explode all trees	2024
	16	MeSH descriptor: [Thyroid Dysgenesis] explode all trees	1
	17	MeSH descriptor: [Thyroid Neoplasms] explode all trees	582
	18	MeSH descriptor: [Neurodevelopmental Disorders] explode all trees	7150
	19	MeSH descriptor: [Learning Disorders] explode all trees	587
	20	MeSH descriptor: [Agnosia] explode all trees	84
	21	MeSH descriptor: [Agraphia] explode all trees	11
	23	MeSH descriptor: [Aphasia] explode all trees	384
	24	MeSH descriptor: [Intellectual Disability] explode all trees	1329
	25	MeSH descriptor: [Neurocognitive Disorders] explode all trees	10105
	26	MeSH descriptor: [Cognitive Dysfunction] explode all trees	1120
	27	MeSH descriptor: [Immune System Diseases] explode all trees	54798
	28	MeSH descriptor: [Hypersensitivity] explode all trees	19545
	29	MeSH descriptor: [Genital Diseases, Male] explode all trees	13646
	30	MeSH descriptor: [Genital Neoplasms, Male] explode all trees	5396
	31	MeSH descriptor: [Genitalia, Male] explode all trees	2016
	32	MeSH descriptor: [Genital Diseases, Female] explode all trees	15775
	33	MeSH descriptor: [Genital Neoplasms, Female] explode all trees	5152
	34	MeSH descriptor: [Genitalia, Female] explode all trees	5124
	35	MeSH descriptor: [Male Urogenital Diseases] explode all trees	37705

Concept	#	Cochrane query	Results
		MeSH descriptor: [Female Urogenital Diseases] explode	
	36	all trees	40677
		#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	163780
	38	#4 AND #7	1
	39	#4 AND #7 AND # 37	0

Clinical Trial Registries

Trial Database	Results	Comment
World Health Organization	104	Completed trials, with results
European Union	7	Completed trials, with results
ISRCTN	18	Completed trials, with results
US Clinical Trials	161	Completed trials, with results
UK Clinical Trials gateway	0	
Health Canada	10	Ongoing trials, no results available

Grey Literature (18 sources)

Resource	Results	Strategy
Agency for Healthcare Research and Quality (AHRQ)	0	Fluoride
CAB Direct	239	Fl, water and outcomes
Canadian Agency for Drugs and Technologies in Health (CADTH)	0	Fluoride
Canadian Public Documents Collection	30	Fluoride (title or abstract)
Centers for Disease Control and Prevention (CDC)	4	
Centre for Reviews and Dissemination (CRD)	0	Fluoride
Conference Board E-Library	0	Fluoride
Environmental Protection Agency (EPA)	2	
Grey Literature Publishers List - International (The New York Academy of Medicine)	0	Fluoride (title or summary)
Grey literature Report	0	Fluoride
Health Quality Ontario	0	Fluoride
Health Systems Evidence	0	Fluoride
National Cancer Institute	2	
National Institute for Health and Care Excellence (NICE)	0	Fluoride
National Library of Medicine (MedlinePlus)	6	Fluoride
National Institutes of Health	3	
TRIP Database	10	Fluoride and water

Resource	Results	Strategy
World Catalogue (Worldcat)	40	Fluoride and water

Section 2. Excluded human studies (with reasons for exclusion)

(Studies arranged by exclusion level, reason for exclusion, then alphabetically by first author's last name)

Le vel	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 (¹⁸ F)-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	Duplicate reference

Level	Bibliography	Reason for exclusion
	in Uruguay <i>Acta Odontol Scand</i> , 78(1), 26-30	
L1	Arnold, W. H.,Gröger, Ch,Bizhang, M.,Naumova, E. A. (2016). Dentin abrasivity of various desensitizing toothpastes <i>Head & face medicine</i> , 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 <i>Environmental geochemistry and health</i> , 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 <i>Annals of agricultural and environmental medicine : AAEM</i> , 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 Canadian population: implications for community water fluoridation <i>Journal of epidemiology and community health</i> , 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 Canadian children: Implications for community water fluoridation Canadian journal of public health = Revue canadienne 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 ¹⁸ F-FDG-PET-CT: phantom validation, practical implications and patient evaluation British Journal of Radiology, 90(1070),	Duplicate reference

Level	Bibliography	Reason for exclusion
	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 [¹⁸ F]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 Canadian 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 kidney injury molecule-1 Environmental Research, 150(#issue#), 653-662	Duplicate reference

Level	Bibliography	Reason for exclusion
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
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.	Duplicate reference

Level	Bibliography	Reason for exclusion
	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 <i>Fluoride</i> , 52(1), 18-28	
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 <i>Chemical communications (Cambridge, England)</i> , 52(36), 6083-6086	Duplicate reference
L1	Choubisaa, S. L. (2018). A brief and critical review of endemic hydrofluorosis in Rajasthan, India <i>Fluoride</i> , 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 <i>Journal of labelled compounds and radiopharmaceuticals. Conference: 22nd international symposium on radiopharmaceutical sciences, ISRS</i> , 60(#issue#), #Pages#	Duplicate reference
L1	Cooray, T., Wei, Y., Zhong, H., Zheng, L., Weragoda, S. K., Weerasooriya, A. R. (2019). Assessment of Groundwater Quality in CKDu Affected Areas of Sri Lanka: Implications for Drinking Water Treatment	Duplicate reference

Level	Bibliography	Reason for exclusion
	International Journal of Environmental Research & Public Health [Electronic Resource], 16(10), 14	
L1	Cooray, T.,Wei, Y.,Zhong, H.,Zheng, L.,Weragoda, S. K.,Weerasooriya, R. (2019). Assessment of groundwater quality in CKDu Affected areas of Sri Lanka: Implications for drinking water treatment International Journal of Environmental Research and Public Health, 16 (10) (no pagination)(1698), #Pages#	Duplicate reference
L1	Cotruvo, Joseph A. (2018). Drinking water contaminants guidebook #journal#, #volume#(#issue#), #Pages#	Duplicate reference
L1	Daiwile, A. P.,Tarale, P.,Sivanesan, S.,Naoghare, P. K.,Bafana, A.,Parmar, D.,Kannan, K. (2019). Role of fluoride induced epigenetic alterations in the development of skeletal fluorosis Ecotoxicol Environ Saf, 169(#issue#), 410-417	Duplicate reference
L1	de Cassia Alves Nunes, R.,Chiba, F. Y.,Pereira, A. G.,Pereira, R. F.,de Lima Coutinho Mattered, M. S.,Ervolino, E.,Louzada, M. J. Q.,Buzalaf, M. A. R.,Silva, C. A.,Sumida, D. H. (2016). Effect of Sodium Fluoride on Bone Biomechanical and Histomorphometric Parameters and on Insulin Signaling and Insulin Sensitivity in Ovariectomized Rats Biological Trace Element Research, 173(1), 144-153	Duplicate reference
L1	Dec, K.,Łukomska, A.,Baranowska-Bosiacka,	Duplicate reference

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	I.,Pilutin, A.,Maciejewska, D.,Skonieczna-Żydecka, K.,Derkacz, R.,Goschorska, M.,W (2018). Pre-and postnatal exposition to fluorides induce changes in rats liver morphology by impairment of antioxidant defense mechanisms and COX induction Chemosphere, 211(#issue#), 112-119	
L1	Dec, K.,Łukomska, A.,Maciejewska, D.,Jakubczyk, K.,Baranowska-Bosiacka, I.,Chlubek, D.,W (2017). The influence of fluorine on the disturbances of homeostasis in the central nervous system Biological Trace Element Research, 177(2), 224-234	Duplicate reference
L1	Dian, B. J.,Selvakumar, R.,Joseph, F. J.,Teresa, M. M.,Thomas, V. P.,Sheshadri, M. S. (2017). 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, 21 (7 Supplement 1)(#issue#), 65	Duplicate reference
L1	Enriquez, J. S.,Yu, M.,Bouley, B. S.,Xie, D.,Que, E. L. (2018). Copper(ii) complexes for cysteine detection using ¹⁹ F magnetic resonance Dalton transactions (Cambridge, England : 2003), 47(42), 15024-15030	Duplicate reference
L1	Escobar-García, Diana,Mejía-Saavedra, Jesús,Jarquín-Yáñez, Lizet,Molina-Frechero, Nelly,Pozos-Guillén, Amaury (2016). Collagenase 1A2 (COL1A2) gene A/C polymorphism in relation to severity of dental fluorosis Community Dentistry &	Duplicate reference

Level	Bibliography	Reason for exclusion
	Oral Epidemiology, 44(2), 162-168	
L1	Fallahzadeh, R. A.,Miri, M.,Taghavi, M.,Gholizadeh, A.,Anbarani, R.,Hosseini-Bandegharai, A.,Ferrante, M.,Oliveri Conti, G. (2018). Spatial variation and probabilistic risk assessment of exposure to fluoride in drinking water Food Chem Toxicol, 113(#issue#), 314-321	Duplicate reference
L1	Farooqi, A.,Sultana, J.,Masood, N. (2017). 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, 33(8), 655-672	Duplicate reference
L1	Fromme, Hermann,Wöckner, Mandy,Roscher, Eike,Völkel, Wolfgang (2017). ADONA and perfluoroalkylated substances in plasma samples of German blood donors living in South Germany International journal of hygiene and environmental health, 220(2 Pt B), 455-460	Duplicate reference
L1	Frood, R.,Baren, J.,McDermott, G.,Bottomley, D.,Patel, C.,Scarsbrook, A. (2018). Diagnostic performance of a streamlined ¹⁸ F-choline PET-CT protocol for the detection of prostate carcinoma recurrence in combination with appropriate-use criteria Clinical Radiology, 73(7), 632-639	Duplicate reference
L1	Frood, R.,McDermott, G.,Scarsbrook, A. (2018). Respiratory-gated PET/CT for pulmonary lesion	Duplicate reference

Level	Bibliography	Reason for exclusion
	characterisation-promises and problems Br J Radiol, 91(1086), 20170640	
L1	Ganyaglo, S. Y.,Gibrilla, A.,Teye, E. M.,Owusu-Ansah, E. D. J.,Tettey, S.,Diabene, P. Y.,Asimah, S. (2019). Groundwater fluoride contamination and probabilistic health risk assessment in fluoride endemic areas of the Upper East Region, Ghana Chemosphere, 233(#issue#), 862-872	Duplicate reference
L1	Ganyaglo, Samuel Y.,Gibrilla, Abass,Teye, Emmanuel M.,Owusu-Ansah, Emmanuel De-Graft Johnson,Tettey, Sampson,Diabene, Perpetual Y.,Asimah, Seyram (2019). Groundwater fluoride contamination and probabilistic health risk assessment in fluoride endemic areas of the Upper East Region, Ghana Chemosphere, 233(#issue#), 862-872	Duplicate reference
L1	Ghosh, S.,Rabha, R.,Chowdhury, M.,Padhy, P. K. (2018). Source and chemical species characterization of PM ₁₀ and human health risk assessment of semi-urban, urban and industrial areas of West Bengal, India Chemosphere, 207(#issue#), 626-636	Duplicate reference
L1	Ghosh, S.,Rabha, R.,Chowdhury, M.,Padhy, P. K. (2018). Source and chemical species characterization of PM ₁₀ and human health risk assessment of semi-urban, urban and industrial areas of West Bengal, India Chemosphere, 207(#issue#),	Duplicate reference

Level	Bibliography	Reason for exclusion
	626-636	
L1	Guissouma, W.,Othman, Hakami,Al-Rajab, A. J.,Tarhouni, J. (2017). Risk assessment of fluoride exposure in drinking water of Tunisia Chemosphere, 177(#issue#), 102-108	Duplicate reference
L1	Hao, Yun-Peng,Liu, Zheng-Yu,Xie, Cheng,Zhou, Lu,Sun, Xun (2016). Novel fluorinated docetaxel analog for anti-hepatoma: Molecular docking and biological evaluation European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 88(#issue#), 274-281	Duplicate reference
L1	Hariri, M.,Mirvaghefi, A.,Farahmand, H.,Taghavi, L.,Shahabinia, A. R. (2018). In situ assessment of Karaj River genotoxic impact with the alkaline comet assay and micronucleus test, on feral brown trout (Salmo trutta fario) Environmental Toxicology & Pharmacology, 58(#issue#), 59-69	Duplicate reference
L1	Hermenegildo, B.,Ribeiro, C.,Pérez-Álvarez, L.,Vilas, José L.,Learmonth, David A.,Sousa, Rui A.,Martins, P.,Lanceros-Méndez, S. (2019). Hydrogel-based magnetoelectric microenvironments for tissue stimulation Colloids and surfaces. B, Biointerfaces, 181(#issue#), 1041-1047	Duplicate reference
L1	Higashiyama, A.,Komori, T.,Juri, H.,Inada, Y.,Azuma, H.,Narumi, Y. (2018). Detectability of residual invasive bladder cancer in delayed ¹⁸ F-	Duplicate reference

Level	Bibliography	Reason for exclusion
	FDG PET imaging with oral hydration using 500 mL of water and voiding-refilling <i>Annals of Nuclear Medicine</i> , 32(8), 561-567	
L1	Hoover, A. J.,Lazari, M.,Ren, H.,Narayanam, M. K.,Murphy, J. M.,van Dam, R. M.,Hooker, J. M.,Ritter, T. (2016). A Transmetalation Reaction Enables the Synthesis of [¹⁸ F]5-Fluorouracil from [¹⁸ F]Fluoride for Human PET Imaging <i>Organometallics</i> , 35(7), 1008-1014	Duplicate reference
L1	Hu, Yueli,Wu, Boyue,Jin, Qing,Wang, Xueyuan,Li, Yan,Sun, Yuxiu,Huo, Jianzhong,Zhao, Xiaojun (2016). Facile synthesis of 5 nm NaYF ₄ :Yb/Er nanoparticles for targeted upconversion imaging of cancer cells <i>Talanta</i> , 152(#issue#), 504-512	Duplicate reference
L1	Iafisco, Michele,Degli Esposti, Lorenzo,Ramírez-Rodríguez, Gloria Belén,Carella, Francesca,Gómez-Morales, Jaime,Ionescu, Andrei Cristian,Brambilla, Eugenio,Tampieri, Anna,Delgado-López, José Manuel (2018). Fluoride-doped amorphous calcium phosphate nanoparticles as a promising biomimetic material for dental remineralization <i>Scientific reports</i> , 8(1), 17016-17016	Duplicate reference
L1	Iarc Working Group on the Evaluation of Carcinogenic Risk to Humans (2017). Some Chemicals Used as Solvents and in Polymer Manufacture #journal#, #volume#(#issue#), #Pages#	Duplicate reference
L1	ISRCTN16831120 (2016). A study to investigate the	Duplicate reference

Level	Bibliography	Reason for exclusion
	<p>effect of a sensitivity toothpaste in providing relief from tooth sensitivity</p> <p>http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN16831120, #volume#(#issue#), #Pages#</p>	
L1	<p>Jack, B.,Ayson, M.,Lewis, S.,Irving, A. ,Agresta, B.,Ko, H. ,Stoklosa, A. (2016). Health Effects of Water Fluoridation: Evidence Evaluation Report. National Health and Medical Research Council, #volume#(#issue#), #Pages#</p>	Duplicate reference
L1	<p>Janka, Z. (2019). [Tracing trace elements in mental functions] Idegyogy Sz, 72(11-12), 367-379</p>	Duplicate reference
L1	<p>Jeong, J. H.,Cho, I. H.,Chun, K. A.,Kong, E. J.,Kwon, S. D.,Kim, J. H. (2016). Correlation Between Apparent Diffusion Coefficients and Standardized Uptake Values in Hybrid ¹⁸F-FDG PET/MR: Preliminary Results in Rectal Cancer Nuclear Medicine and Molecular Imaging, 50(2), 150-156</p>	Duplicate reference
L1	<p>Jiang, F.,Lei, P.,Chen, Y.,Zuu, X.,Lao, P.,Pan, X. (2017). Quantitative computed tomography measurement skeletal fluorosis rabbits bone density and the correlation with bone injury. [Chinese] Chinese Journal of Endemiology, 36(6), 414-417</p>	Duplicate reference
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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 visualization Sci Total Environ, 698(#issue#), 134168	Used reference concentration
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.	Used reference

Level	Bibliography	Reason for exclusion
	<p>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</p>	concentration
L2	<p>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 drinking water and associated health risks in a semiarid region of Northern China Ecotoxicol Environ Saf, 171(#issue#), 274-280</p>	Used reference concentration
L2	<p>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</p>	Used reference concentration
L2	<p>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</p>	Used reference concentration

Section 3. 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 ^[1]

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 Sex: Girls: 34.52% Exclusions:	Exposures: <u>Fluoride levels in:</u> <ul style="list-style-type: none"> • Ground water Method of exposure assessment: <ul style="list-style-type: none"> • SPANDS method Exposure level(s): <ul style="list-style-type: none"> • <u>Ground water (mg/L)</u> 0.22-0.98 mg/L 	Outcome(s): <ul style="list-style-type: none"> • Dental fluorosis Method of outcome ascertainment: <ul style="list-style-type: none"> • Dean's index 	Statistical analysis: <ul style="list-style-type: none"> • Descriptive analysis Results: <u>Fluoride in water/Dean's fluorosis index:</u> Panchacutes I: 0.98mg/L/2.08 Tiabaya Pampas Nuevas: 0.79 mg/L/1.90 Tiabaya El Cural: 0.73 mg/L/1.72 La Bedoya: 0.43 mg/L/1.54	"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
<ul style="list-style-type: none"> • Students with an oral pathology treatment • Live in a different region of the school <p>Source of funding / support: NR</p> <p>Author declaration of interest: NR</p>			<p>Panchacutes II: 0.32 mg/L/1.42</p> <p>La Tomialla: 0.22 mg/L/1.26</p> <p><u>Dental fluorosis for Panchacutes I:</u> Severe: 10.71% Moderate: 23.81% Mild: 32.14% Very Mild: 26.19% Questionable: 7.143 % Normal: 0%</p> <p><u>Tiabaya Pampas Nuevas:</u> Severe: 8.33% Moderate: 21.43% Mild: 30.95% Very Mild: 26.19% Questionable: 9.52 % Normal: 3.57%</p> <p><u>Tiabaya "El Cural":</u> Severe: 5.95% Moderate: 19.05% Mild: 29.76% Very Mild: 26.19% Questionable: 10.71 % Normal: 8.33%</p> <p><u>La Bedoya:</u> Severe: 3.57% Moderate: 15.48% Mild: 29.76% Very Mild: 27.38%</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			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: ($p < 0,05$; $\chi^2 < 0,05$) 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	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			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%	
			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		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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
	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

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

Tang 2023 [\[2\]](#)

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	Exposures: <u>Fluoride levels in:</u> <ul style="list-style-type: none"> Ground water Urine samples Method of exposure assessment: <ul style="list-style-type: none"> <u>Fluoride in Drinking water and Urine samples:</u> Ion-selective potentiometry (PF-202-CF; INESA 	Outcome(s): <ul style="list-style-type: none"> Dental fluorosis 	Statistical analysis: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> <u>Water fluoride concentration >1mg/L and DF prevalence:</u> Normal: 17 (5.6%) Very mild: 47 (15.5%) Mild: 210 (69.3%) Moderate: 29 (9.6%) <u>Water fluoride concentration</u> 	<ul style="list-style-type: none"> 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 593</p> <p>Sex: N (%): Girls: 300 (50.6%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • 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. <p>Source of funding / support:</p> <ul style="list-style-type: none"> • National Natural Science Foundation of China (Grants No. 82073515, and No. 81773388) • The State Key Program of National Natural Science Foundation of 	<p>Scientific Instrument Co., Ltd., China)</p> <p>Exposure level(s): (Chinese standard fluoride limit in water = 1.0mg/L)</p> <ul style="list-style-type: none"> • 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 • <u>Fluoride concentration.: Mean :</u> SD ($\geq 1\text{mg/L}$): Higher exposure gp.: Water: 2.19 \pm0.81 Urine: 2.48 \pm0.88 <u>Lower exposure gp.:</u> Water: 0.61 \pm0.24 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Dean's Index 	<p><u>1mg/L and DF prevalence:</u> Normal: 216 (74.5%) Very mild: 22 (15.2%) Mild: 30 (10.3%) Moderate:0(0.00%)</p> <ul style="list-style-type: none"> • <u>Water fluoride and DF (PR (95% CI), increase per 1ml/L):</u> 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 • <u>Urinary fluoride DF (PR (95% CI), increase per 1ml/L):</u> 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 <p><u>Association between fluoride content and DF by sex: PR (95%CI)</u> <u>Water Fluoride</u> Overall: 1.33 (1.29, 1.36), P-interaction=0.325 Very Mild: 1.31 (1.23, 1.39) P-interaction=0.485</p>	<p>exposure.</p> <ul style="list-style-type: none"> • The study demonstrates that the risk of DF has an upward trend when the fluoride gradually in increases, in water and urine.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
China (Grant No. 81430076) Author declaration of interest: No COI	Urine: 0.18 ±0.12		Mild: 1.39 (1.35, 1.44) P-interaction=0.431 Moderate: 1.33 (1.25, 1.42) P-interaction=0.852 <i>Urinary Fluoride:</i> 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> <i>Adjusted for age and sex, water fluoride (mg/L)</i> 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) * 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) *	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><i>Adjusted for BMI, water fluoride (mg/L)</i></p> <p>Overall: 1.50 (1.42, 1.58) WHO Guideline: 0.79 (0.67, 0.91) *</p> <p>Very Mild: 1.82 (1.62, 2.05) WHO Guideline: 1.23 (0.95, 1.51) *</p> <p>Mild: 1.72 (1.61, 1.83) WHO Guideline: 1.11 (0.94, 1.28) *</p> <p>Moderate: 3.27 (2.73, 3.92) WHO Guideline: 3.15 (2.40, 3.90) *</p> <p><i>Adjusted for parental education, and family income, water fluoride (mg/L)</i></p> <p>Overall: 1.50 (1.43, 1.58) WHO Guideline: 0.79 (0.67, 0.91) *</p> <p>Very Mild: 1.83 (1.63, 2.06) WHO Guideline: 1.22 (0.95, 1.50) *</p> <p>Mild: 1.73 (1.62, 1.84) WHO Guideline: 1.11 (0.94, 1.28) *</p> <p>Moderate: 3.78 (2.93, 4.88) WHO Guideline: 3.12 (2.29, 3.95) *</p> <p><i>Adjusted for low birth weight, water fluoride (mg/L)</i></p> <p>Overall: 1.50 (1.42, 1.57)</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>WHO Guideline: 0.79 (0.67, 0.91) *</p> <p>Very Mild: 1.83 (1.62, 2.06)</p> <p>WHO Guideline: 1.21 (0.92, 1.50) *</p> <p>Mild: 1.72 (1.61, 1.83)</p> <p>WHO Guideline: 1.11 (0.94, 1.28) *</p> <p>Moderate: 3.384 (2.82, 4.07)</p> <p>WHO Guideline: 3.13 (2.37, 3.89) *</p> <p><i>Adjusted for age, sex, BMI, parental education, family income, and low birth weight, water fluoride (mg/L)</i></p> <p>Overall: 1.50 (1.42, 1.58)</p> <p>WHO Guideline: 0.78 (0.66, 0.90) *</p> <p>Very Mild: 1.85 (1.64, 2.07)</p> <p>WHO Guideline: 1.24 (0.95, 1.52) *</p> <p>Mild: 1.723 (1.61, 1.84)</p> <p>WHO Guideline: 1.10 (0.93, 1.27) *</p> <p>Moderate: 3.92 (3.03, 5.06)</p> <p>WHO Guideline: 3.13 (2.32, 3.94) *</p> <p>*Water fluoride \leq 1.5 is reference. P=0.001</p> <p><u>Sensitivity analysis for effect of fluoride exposure on DF: [PR (95%CI) for every 1mg/L</u></p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<u>increment of urinary fluoride]</u> <i>Adjusted for age and sex, urinary fluoride (mg/L)</i> 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)	
			<i>Adjusted for BMI, urinary fluoride (mg/L)</i> Overall: 1.41 (1.34, 1.48) Very Mild: 1.63 (1.44, 1.85) Mild: 1.57 (1.47, 1.67) Moderate: 2.59 (2.18, 3.08)	
			<i>Adjusted for parental education, and family income, urinary fluoride (mg/L)</i> 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)	
			<i>Adjusted for low birth weight, urinary fluoride (mg/L)</i> 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)	
			<i>Adjusted for urinary creatinine, urinary fluoride (mg/L)</i> Overall: 1.42 (1.35, 1.50) Very Mild: 1.63 (1.43, 1.86)	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			Mild: 1.59 (1.48, 1.71) Moderate: 2.76 (2.19, 3.48) <i>Adjusted for age, urine creatinine, sex, BMI, parental education, family income and low birth weight, urinary fluoride (mg/L)</i> 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.	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 (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 using 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross-sectional study Country: Pakistan Participants: Students (9 – 11 years of age) of madrassa (Islamic religious school) in urban and rural locations within the province of Sindh Sampling time frame:	Exposures: <u>Fluoride levels in</u> <ul style="list-style-type: none"> • Drinking water • Urine Method of exposure assessment: NR Exposure level: <u>Mean fluoride levels in urban madrassas (Karachi Central)</u> <ul style="list-style-type: none"> • Drinking water: 2.04 mg/L • Urine: 5.99 (\pm3.57) mg/L <u>Mean fluoride levels in rural madrassas (Umerkot)</u>	Outcome(s): <ul style="list-style-type: none"> • IQ Method of outcome ascertainment: <ul style="list-style-type: none"> • The Raven's Progressive Matrices Intelligence Test • A teacher trained by a psychologist administered the test 	Statistical analysis: <ul style="list-style-type: none"> • 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 <u>IQ <70 retarded (low)</u> <ul style="list-style-type: none"> • High fluoride: 2 (3.33) • Low fluoride: 5 (8.33) <u>IQ 70 – 79 borderline (below average)</u> <ul style="list-style-type: none"> • High fluoride: 4 (6.67) • Low fluoride: 6 (10) <u>IQ 80 – 89 dull normal (low average)</u> <ul style="list-style-type: none"> • High fluoride: 10 (16.67) 	<ul style="list-style-type: none"> • “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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
NR	<ul style="list-style-type: none"> • Drinking water: 1.07 mg/L • Urine: 3.53 (±1.09 mg/L) 		<ul style="list-style-type: none"> • Low fluoride: 9 (15) 	<p>were not controlled for in the present study, including the level of parental education, socio-economic status, and the levels of arsenic, lead, and iodine.” (p. 57)</p>
Sample size:			<u>IQ 90 – 109 normal (average)</u>	
120			<ul style="list-style-type: none"> • High fluoride: 20 (33.33) • Low fluoride: 19 (31.67) 	
Sex N (%):			<u>IQ 110 – 119 bright normal (high average)</u>	
Girls: 34 (28.3%)			<ul style="list-style-type: none"> • High fluoride: 16 (26.67) • Low fluoride: 15 (25) 	
Exclusions:			<u>IQ 120 – 129 superior (good)</u>	
NR			<ul style="list-style-type: none"> • High fluoride: 7 (11.67) • Low fluoride: 6 (10) 	
Source of funding / support:			<u>IQ >129 very superior (excellent)</u>	
NR			<ul style="list-style-type: none"> • High fluoride: 1 (1.66) • Low fluoride: 0 (0.0) 	
Author declaration of interest:				
NR			<p>“No significant difference was present between the IQ distribution in the high and low fluoride areas on chi-</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>square testing after 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)</p> <p>IQ scores by high (urban) and low (rural) fluoride areas stratified by gender</p> <p><u>Boys</u></p> <ul style="list-style-type: none"> • High fluoride: 99.95 (± 15.50) • Low fluoride: 92.30 (± 14.97) <p><u>Girls</u></p> <ul style="list-style-type: none"> • High fluoride: 96.90 (± 16.31) • Low fluoride: 90.30 (± 15.49) <p>“comparing IQ of high</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			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
	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

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
		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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride level(s) in:</u>	Outcome(s): • Intelligence quotient (IQ).	Statistical analysis: • Descriptive analysis • Generalized linear model (GLM) • Multinomial logistic regression	<ul style="list-style-type: none"> • “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 design: Cross-sectional	• Urine			
Country: China				
Participants: Children aged 8-12 years	Method of exposure assessment:		Results: Mean IQ scores	
Sampling time frame: April-May 2017	• Fluoride ion-selective electrode (Shanghai Exactitude Instruments, Shanghai, China)		• HFG: 122.61±11.61 • CG: 121.50±12.14 • P=0.290 • Total: 122.05±11.88	
Sample size: 683	• Creatinine-adjusted urinary fluoride (UFcr) levels were calculated		Distribution by intelligence level in HFG and CG • Normal (IQ 90-109): 15.25% (HFG); 17.54% (CG) • 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)	
Sex: N (%): Boys: 324 (47.44%)	Exposure level(s): Median UFcr (mg/L): 1.33	Method of outcome ascertainment:		
Exclusions: • Non-residents	Children were divided into two groups, high	• The second revision of the Combined Raven’s Test – the Rural in China		

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> On calcium supplements Had disorders of calcium or phosphorus metabolism, digestive diseases, or thyroid diseases. Children with IQ<90 <p>Source of funding / support:</p> <ul style="list-style-type: none"> The National Natural Science Foundation of China (Nos. 81972981, 82003401, and 81673116) Key Projects of Colleges and Universities of Henan Education Department (21A330006) <p>Author declaration of interest: no COI</p>	<p>fluoride group (HFG, UFcr>1.33 mg/L) and control group (CG, UFcr≤1.33 mg/L).</p> <p>Mean urinary fluoride [UF, unadjusted for creatinine] (mg/L):</p> <ul style="list-style-type: none"> HFG: 1.56±0.82 CG: 0.98±0.62 P<0.001 Total: 1.27±0.79 <p>Mean UFcr (mg/L)</p> <ul style="list-style-type: none"> HFG: 2.15±0.91 CG: 0.83±0.30 P<0.001 Total: 1.49±0.95 	<p>(CRTRC2)</p> <ul style="list-style-type: none"> Children completed the test “independently with the supervision of trained investigators”. 	<ul style="list-style-type: none"> P=0.539 <p>High fluoride group (HFG)</p> <ul style="list-style-type: none"> Change in IQ score per 1.0 mg/L increase in UFcr level: $\beta=-2.502$ (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 <p>Control group</p> <ul style="list-style-type: none"> 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 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>Total</p> <ul style="list-style-type: none"> • 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 ($IQ \geq 130$) 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); $p=0.426$ <p><u>Statistically significant gene-environmental interaction on the IQ scores</u></p> <p><i>[Polymorphisms in 4 loci of MTHFD1 related to neurodevelopment (rs11627387, rs1076991, rs2236224, and rs2236225) were analyzed]</i></p> <ul style="list-style-type: none"> • 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 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			rs1076991 x rs2236224 x rs2236225: F=1.614; p=0.012	

Risk of bias assessment				
<i>Bias domain</i>	<i>Criterion</i>		<i>Response</i>	
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	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
	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 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	Were all measured outcomes reported?	++	Yes, the primary outcome (children intelligence, IQ)

Risk of bias assessment				
<i>Bias domain</i>	<i>Criterion</i>			<i>Response</i>
reporting				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

García-Escobar 2022 [\[5\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride levels in</u>	Outcome(s): Dental fluorosis	Statistical analysis: • Fisher's exact test	• "Patients from rural communities of the
Study design: Cross-sectional	• Drinking water		• Spearman's rank order correlation	Anantapur district showed a high
Country: India			• Method for estimation of ORs not reported.	prevalence (over 90%) of dental
Participants: 785 subjects aged 10-60 years	Method of exposure assessment:		Results: <u>Overall prevalence</u>	fluorosis. Moreover, the Anantapur population presents

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sampling time frame: NR</p> <p>Sample size: 785</p> <p>Sex: N (%): Men: 322 (41.3%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Orofacial malformations or pathologies that could make examination difficult • Systemic pathology affecting fluoride metabolism • Absence of permanent or definitive teeth • Dental surface wear or 	<ul style="list-style-type: none"> • Fluoride levels in water: “ion chromatography according to the parameters for potable waters for public consumption in Spain (R.D. 140/2003)” <p>Exposure level(s):</p> <ul style="list-style-type: none"> • Water fluoride (ppm): 1.1 to 2.92 (mean 1.71, median 1.5) 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • The Dean Index (DI) • The Thylstrup and Fejerskov Index (TFI) 	<ul style="list-style-type: none"> • 94.6% (DI) • 94.4 (TFI) <p><u>Prevalence of Moderate–Severe (MS) cases (DI) and TFI score 4–9 cases</u></p> <p>[DI MS group corresponds to TFI 4–9]</p> <ul style="list-style-type: none"> • 62.8% (DI MS) • 73.1% (TFI 4-9) <p><u>Prevalence of fluorosis among those consuming water with water fluoride ≤1.5 ppm</u></p> <ul style="list-style-type: none"> • 54.3% (DI) • 54.5% (TFI) <p><u>Prevalence of DI MS and TFI 4-9 among those consuming water with water fluoride ≤1.5 ppm</u></p> <ul style="list-style-type: none"> • 33.2% (DI MS) • 39.9% (TFI 4-9) <p><u>OR (95% CI)</u></p>	<p>a high number of moderate and severe cases (over 60%), while other populations showed less severe forms of fluorosis, despite reporting superior fluoride levels to those found in the Anantapur drinking water.”</p> <ul style="list-style-type: none"> • “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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>stains due to tobacco, betel, or another chewing habit</p> <ul style="list-style-type: none"> • 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. <p>Source of funding / support: No external funding</p> <p>Author declaration of interest: No COI</p>			<p>DI MS</p> <ul style="list-style-type: none"> • ≤1.5 ppm: reference • >1.5 ppm: 1.81 (1.34–2.45) • P=0.000 <p>TFI 4-9</p> <ul style="list-style-type: none"> • ≤1.5 ppm: reference • >1.5 ppm: 1.79 (1.28–2.5) • P=0.000 <p>Spearman's rank order correlation between water fluoride and moderate-severe fluorosis</p> <ul style="list-style-type: none"> • DI MS: $R_s=0.527$; $p=0.064$ • TFI 4-9: $R_s=0.610$; $p=0.027$ 	<p>observed. A potential change in the biological susceptibility of the population to the toxin, due to the long-term exposition (including several generations) could explain the phenomenon..."</p>

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?	-	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 Thylstrup 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		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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 [\[6\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cohort (ELEMENT) Country: Mexico	Exposures: <u>Fluoride level in</u> <ul style="list-style-type: none"> Maternal urine collected during one or more trimesters of pregnancy 	Outcome(s): <ul style="list-style-type: none"> Children's IQ 	Statistical analysis: <ul style="list-style-type: none"> 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) 	<ul style="list-style-type: none"> "... 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-point decrement in children's Full-Scale IQ scores".

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants:</p> <ul style="list-style-type: none"> 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 <p>Sampling time frame:</p> <p>Recruitment: Cohort 2A in 1997-1999; Cohort 3 in 2001-2003</p> <p>Sample size:</p>	<p>Method of exposure assessment:</p> <ul style="list-style-type: none"> 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. 		<p>Results:</p> <p>Changes in cognitive score per 0.5 mg/L increase in MUFcre</p> <p><u>GEE population-averaged models</u></p> <ul style="list-style-type: none"> 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) <p><u>Linear regression analysis</u></p> <p>Age 4</p> <ul style="list-style-type: none"> 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 VIQ: B=-0.81 (95% CI: -2.30, 0.69); p>0.05 <p>Age 5</p> <ul style="list-style-type: none"> GCI: B=-1.97 (95% CI: -3.64, - 	<ul style="list-style-type: none"> “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
<ul style="list-style-type: none"> • 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 	<p>Exposure level(s):</p> <ul style="list-style-type: none"> • Creatinine-adjusted maternal urinary fluoride (MUFcre, µg/L): 0.14 to 3.01; mean 0.90 (SD 0.39), 	<p>Method of outcome ascertainment:</p> <p>McCarthy Scales of Children’s Abilities (MSCA) translated into Spanish to children aged 4 and 5 years</p> <ul style="list-style-type: none"> • Verbal scale (VIQ, a 	<p>0.30); p=0.021</p> <ul style="list-style-type: none"> • 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 <p>Age 6-12</p> <ul style="list-style-type: none"> • 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 <p><u>Sensitivity analyses (GEE models),</u> <u>B (95% CI)</u></p> <p>FSIQ/GCI.</p> <ul style="list-style-type: none"> • Model A⁵: -2.10 (-3.47, -0.73) • Model A + number/timing of urine samples⁶: -2.12 (-3.49, -0.75) 	

⁵ 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.

⁶ Number/timing of urine samples included as a covariate

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Age 6-12: 132 (47.48%) <p>Exclusions:</p> <p>Women with a history of psychiatric disorders, substance use, high-risk pregnancy, or other medical conditions</p>	<p>median 0.83; IQR 0.64-1.11</p>	<p>measure of verbal reasoning and comprehension)</p> <ul style="list-style-type: none"> • Perceptual-performance scale (PIQ, a measure of nonverbal reasoning and perceptual information processing) • General Cognitive Index (GCI), the standardized composite score <p>Spanish version of Wechsler Abbreviated Scale of Intelligence (WASI) to children aged 6-12 years.</p> <ul style="list-style-type: none"> • Verbal IQ (VIQ, a 	<ul style="list-style-type: none"> • Model A – IQ score<70⁷: -1.67 (-2.93, -0.41) • Model A – Cohort 3 Ca⁸: -1.98 (-3.70, -0.27) • Model A – Maternal IQ⁹: -2.40 (-3.79, -1.01) • Model A + Maternal IQ¹⁰: -2.09 (-3.44, -0.73) • Model A – HOME¹¹: -2.33 (-4.46, -0.20) • Model A + HOME¹²: -2.11 (-4.06, -0.16) • Model A – Patella Lead¹³: -2.42 (-3.98, -0.86) • Model A + Patella Lead¹⁴: -2.41 (-3.98, -0.85) • Model A – Tibia Lead¹⁵: -2.75 (-4.61, -0.89) 	

⁷ Excluding cases with FSIQ/GCI, PIQ, or VIQ scores less than 70

⁸ Subset of cases who received calcium supplementation

⁹ Subset of cases who have data on maternal IQ

¹⁰ Subset of cases who have data on maternal IQ, adjusted for maternal IQ

¹¹ Subset of cases who have data on Home Observation for the Measurement of the Environment (HOME) scores

¹² Subset of cases with HOME score, adjusted for HOME score

¹³ Subset of cases who have data on maternal patella lead

¹⁴ Subset of cases with data on maternal patella lead, adjusted for maternal patella lead

¹⁵ Subset of cases who have data on maternal tibia lead

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding / support:</p> <ul style="list-style-type: none"> • The American British Cowdray Hospital provided facilities for the ELEMENT research. • U.S. National Institutes of Health (NIH; grants R01ES021446 and R01-ES007821) • The National Institute of Environmental 		<p>measure of verbal reasoning and comprehension)</p> <ul style="list-style-type: none"> • Performance (PIQ, a measure of nonverbal reasoning and spatial processing) • Full-Scale intelligence (FSIQ, a measure of global intellectual functioning) <p>Each child was evaluated by one of three psychologists supervised by experienced developmental psychologist.</p> <p>The inter-examiner reliability: $r > 0.90$ (MSCA); not assessed for WASI</p>	<ul style="list-style-type: none"> • Model A + Tibia Lead¹⁶: -2.23 (-4.09, -0.38) • Model A – Tibia and Patella Lead¹⁷: -2.73 (-4.71, -0.76) • Model A + Tibia and Patella Lead¹⁸: -2.20 (-4.18, -0.22) <p>PIQ</p> <ul style="list-style-type: none"> • 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) 	

¹⁶ Subset of cases with data on maternal tibia lead, adjusted for maternal tibia lead

¹⁷ Subset of cases who have data on maternal tibia and patella lead

¹⁸ 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
<p>Health Sciences/the U.S. Environmental Protection Agency (NIEHS/EPA; grant P01ES022844, 83543601)</p> <ul style="list-style-type: none"> • The NIEHS (grant P42-ES05947, P20ES018171) • NIEHS Center Grant P30ES017885) • National Institute of Public Health/Ministry of Health of Mexico 			<ul style="list-style-type: none"> • 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) • Model A – Tibia and Patella Lead: -2.75 (-4.50, -1.00) • Model A + Tibia and Patella Lead: -2.32 (-4.08, -0.56) <p>VIQ</p> <ul style="list-style-type: none"> • 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
declaration of interest: No COI			<ul style="list-style-type: none"> • 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

<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 fluoride exposure level. Time frame was different for

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
			the two cohorts (2A and 3). More information about study participants can be found in Perng et al. 2019 ¹⁹ .
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 pregnancy, or other medical conditions). Although it is not reported, there is no indication that losses to

¹⁹ <https://bmjopen.bmj.com/content/9/8/e030427>

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
		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).
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

Risk of bias assessment				
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>		
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 [\[7\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Case-Control Study Country: India Participants: Subjects: from endemic villages, controls: from	Exposures: <u>Fluoride levels in:</u> <ul style="list-style-type: none"> • Drinking water • Serum Method of exposure assessment:	Outcome(s): <ul style="list-style-type: none"> • Dental fluorosis • Skeletal fluorosis 	Statistical analysis: <ul style="list-style-type: none"> • Descriptive analysis • Analysis of variance Results: Water fluoride concentration	<ul style="list-style-type: none"> • “Besides high concentrations of fluoride in potable water, poor socio-economic status and nutritional deficiency also contribute to fluorosis in exposed individuals from endemic regions.” • For the individuals

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>non-endemic villages</p> <p>Sampling time frame: 2014-2015</p> <p>Sample size: 180</p> <p>Sex: N (%): NR</p> <p>Exclusions: Neonates, children, pregnant women and patients with other severe & chronic diseases</p> <p>Source of funding / support:</p> <ul style="list-style-type: none"> • UGC, New Delhi • Chhattisgarh Council of Science and Technology <p>Author declaration of interest: No COI</p>	<ul style="list-style-type: none"> • Drinking water: Thermo scientific orion 9609 BNWP ion selective fluoride electrode • Serum: Semi auto analyzer (Model CHEM 400), Electronics India. <p>Exposure level(s):</p> <ul style="list-style-type: none"> • <u>Mean drinking water fluoride levels</u> 1.16-7.56 ppm 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • <u>Dental Fluorosis:</u> NR • <u>Skeletal Fluorosis:</u> NR 	<p>associated with:</p> <ul style="list-style-type: none"> • Dental fluorosis: 0.67-0.83 ppm • Skeletal fluorosis: 0.43-0.83 ppm 	<p>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 preliminary screening for those individuals. However, urine and blood fluoride analyses of the subjects are also needed for further confirmation."</p>

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	
	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	Were all measured outcomes reported?	++	Yes, the primary outcomes discussed in methods were	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
reporting		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 ^[8]

Ibarluzea 2022				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Routes of exposures:	Outcome(s): • Children's cognition/intelligence	Statistical analysis ²⁰ : • 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,
Study design: Longitudinal	<u>Fluoride level in</u> • Maternal urine			
Country: Spain	collected in the first and third trimesters			

²⁰ Student's t-test, one-way ANOVA and Pearson correlation were used to select variables for multiple linear regression (with p<0.2)

	of pregnancy				performance,
Participants:	Method of exposure		Results:		numeric, memory
Pregnant women	assessment:		Changes in cognitive score		scores and GCI, in
Children examined at	• Potentiometry using		per unit (mg/g) increase in		boys at the age of 4
ages 1 and 4 years	an ion-selective		maternal creatinine-adjusted		years, although
Sampling time frame:	electrode (DX219-F,		urinary fluoride (MUFcr), β		when Hg levels were
Recruitment of pregnant	Mettler Toledo)		(95% CI)²¹		included in the
women between 1997	• Urinary fluoride		<u>Bayley Mental Development</u>		model only verbal
and 2008 in different	levels were adjusted		<u>Index (MDI)</u>		and GCI at week 32
study areas (Guxen et	for creatinine		<i>Both trimesters MUFcr</i>		and whole
al. 2012) ²²			• All: 1.48 (-4.2, 7.16)		pregnancy remained
Sample size:			• Boys: 3.84 (-5.04, 12.72)		significant or
• Assessed at age 1			• Girls: 0.75 (-6.92, 8.43)		marginally
year: 316 mother-child			<i>Week 12 MUFcr</i>		significant.”
pairs			• All: 0.55 (- 4.64, 5.74)		• “The positive
• Assessed at ages 1 and			• Boys: 2.96 (-5.09, 11.01)		associations
4 years: 248 mother-			• Girls: -1 (-8.07, 6.07)		between MUFcr and
child pairs			<i>Week 32 MUFcr</i>		cognitive functions
Sex: N (%):	Exposure level(s):	Method of outcome	• All: 1.52 (-2.92, 5.97)		seemed to be more

²¹ 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

²² 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

<p>Boys:</p> <ul style="list-style-type: none"> Assessed at age 1 year: 146 (46.2%) Assessed at age 4 years: 125 (50.4%) <p>Exclusions:</p> <p><u>At recruitment</u></p> <ul style="list-style-type: none"> Maternal age <16 years Multiple pregnancy Pregnancy achieved with assisted reproduction techniques Not planning birth in the referral hospital Communication problems in Spanish or Basque <p><u>Analytical sample</u></p> <ul style="list-style-type: none"> Incomplete data [To be included, participants had to have 1) data on 	<p>Fluoride levels in drinking water</p> <ul style="list-style-type: none"> Community fluoridated drinking water systems: mean 0.81 (SD 0.15) mg/L Community non-fluoridated drinking water systems: <0.1 mg/L <p>Mean (95% CI) maternal creatinine-adjusted urinary fluoride levels (mg/g creatinine)²³</p> <p><u>Assessed at age 1 year</u></p> <ul style="list-style-type: none"> Both trimesters: 0.66 (0.61; 0.70) Week 12 of pregnancy: 0.57 	<p>ascertainment:</p> <ul style="list-style-type: none"> Bayley Scales of Infant Development (BSID) at age 1 year McCarthy Scales of Children's Abilities (MSCA)²⁴ 	<ul style="list-style-type: none"> Boys: 2.50 (-4.46, 9.46) Girls: 1.7 (-4.30, 7.71) <p><u>McCarthy, verbal</u></p> <p>Both trimesters MUFcr</p> <ul style="list-style-type: none"> All: 13.86 (3.91, 23.82) Boys: 13.38 (2.81, 23.95) Girls: -1.31 (-9.35, 6.74) P<0.05 <p>Week 12 MUFcr</p> <ul style="list-style-type: none"> All: 1.11 (-4.86, 7.07) Boys: 3.78 (-6.16, 13.71) Girls: -0.91 (-8.78, 6.96) <p>Week 32 MUFcr</p> <ul style="list-style-type: none"> All: 12.01 (4.82, 19.19) Boys: 11.79 (4.22, 19.36) Girls: -0.93 (-7.01, 5.15) P<0.01 <p><u>McCarthy, performance</u></p> <p>Both trimesters MUFcr</p> <ul style="list-style-type: none"> All: 5.86 (0.32, 11.39) 	<p>evident in children of mothers who lived their pregnancy in the nonfluoridated zones.”</p> <ul style="list-style-type: none"> “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 associations in the
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²³ Detailed data on maternal creatinine-adjusted urinary fluoride levels by maternal and children's characteristics are reported in Supplementary tables S2, S3 and S5

²⁴ The motor scale of the MSCA was not included in this study.

<p>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.]</p>	<p>(0.52; 0.62)</p> <ul style="list-style-type: none"> • Week 32 of pregnancy: 0.74 (0.69; 0.79) • P<0.001 [1st vs. 3rd trimester] <p><u>Assessed at age 4 years</u></p> <ul style="list-style-type: none"> • Both trimesters: 0.64 (0.59; 0.68) • Week 12 of pregnancy: 0.55 (0.50;0.60) 	<ul style="list-style-type: none"> • Boys: 12.24 (2.87, 21.61) • Girls: 2.03 (-4.77, 8.83) • P<0.05 <p>Week 12 MUFcr</p> <ul style="list-style-type: none"> • All: 4.63 (-0.57, 9.82) • Boys: 9.11 (0.47, 17.75) • Girls: 1.10 (-5.53, 7.73) <p>Week 32 MUFcr</p> <ul style="list-style-type: none"> • All: 3.68 (-0.49, 7.85) • Boys: 7.17 (0.24, 14.09) • Girls: 1.69 (-3.44, 6.83) • P<0.05 <p><u>McCarthy, numeric</u></p> <p>Both trimesters MUFcr</p> <ul style="list-style-type: none"> • All: 6.22 (0.65, 11.79) • Boys: 11.09 (1.79, 20.4) • Girls: 3.03 (-3.96, 10.03) • P<0.05 <p>Week 12 MUFcr</p> <ul style="list-style-type: none"> • All: 4.47 (-0.79, 9.73) • Boys: 5.03 (-3.65, 13.7) • Girls: 2.92 (-3.95, 9.78) 	<p>first trimester indicate that the effects are associated with later periods in pregnancy.”</p> <ul style="list-style-type: none"> • “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
<p>Source of funding / support²⁵:</p> <ul style="list-style-type: none"> • The Instituto de Salud Carlos III, Red de Centros de investigación en Epidemiología y Salud Pública (RCESP) • CIBER Epidemiología y Salud Pública 	<ul style="list-style-type: none"> • Week 32 of pregnancy: 0.73 (0.67;0.79) • P<0.001 [1st vs. 3rd trimester] <p>Whole pregnancy mean (SD) maternal urinary fluoride (mg/L)</p>		

²⁵ Information from Guxen et al. 2012.

(CIBERESP)	<u>Assessed at age 1</u>	Week 32 MUFcr	prospective studies.”
• The Fondo de Investigación Sanitaria	<u>year</u>	• All: 4.13 (-0.07, 8.32)	
• The European Union’s 6th and 7th Framework Programmes (Hiwate, Escape, Hitea and Contamed projects)	• Non-fluoridated zone: 0.36 (0.21) • Fluoridated zone: 0.65 (0.29) • P<0.001	• Boys: 8.56 (1.81, 15.31) • Girls: 1.55 (-3.74, 6.85) • P<0.05	
• The Ministerio de Educación y Ciencia, the Generalitat de Catalunya	<u>Assessed at age 4</u>	<u>McCarthy, memory</u>	
• The Centre for Research in Environmental Epidemiology (CREAL) of Barcelona	<u>years</u>	Both trimesters MUFcr	
• The Fundació La Caixa, the Fundació Roger Torné	• Non-fluoridated zone: 0.35 (0.20) • Fluoridated zone: 0.62 (0.26) • P<0.001	• All: 11.63 (2.62, 20.63) • Boys: 11.3 (1.90, 20.7) • Girls: -2.12 (-9.32, 5.09) • P<0.05	
• The Consejería de Salud de Andalucía	Both trimesters mean (SD) creatinine-adjusted maternal urinary fluoride (mg/g creatinine)	Week 12 MUFcr	
• The Junta the Andalucía	<u>Assessed at age 1</u>	• All: 1.71 (-3.66, 7.09) • Boys: 4.28 (-4.51, 13.06) • Girls: -1.40 (-8.46, 5.67)	
• The Conselleria de	<u>year</u>	Week 32 MUFcr	
	• Non-fluoridated zone: 0.46 (0.25) • Fluoridated zone:	• All: 9.2 (2.67, 15.73) • Boys: 9.26 (2.47, 16.05) • Girls: -1.72 (-7.17, 3.72) • P<0.01	
		<u>McCarthy, general cognitive</u>	
		Both trimesters MUFcr	
		• All: 15.4 (6.32, 24.48) • Boys: 15.03 (5.3, 24.75)	

Sanitat de la Generalitat Valenciana	0.84 (0.40) • P<0.001	• Girls: -0.02 (-7.16, 7.12) • P<0.01
• The CAJASTUR—Caja Asturias	<u>Assessed at age 4 years</u>	Week 12 MUFcr • All: 3.37 (-2.09, 8.83) • Boys: 7.14 (-2.06, 16.33) • Girls: 0.21 (-6.77, 7.19)
• The Spanish Association against the Cancer (AECC) (Delegación Provincial Asturias)	• Non-fluoridated zone: 0.45 (0.26) • Fluoridated zone: 0.82 (0.39) • P<0.001	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
• The Departamento de Sanidad-Gobierno Vasco		Changes in cognitive score per unit (mg/g) increase in MUFcr, β (95% CI) <u>additionally adjusted for cord blood Hg levels.</u>
• The Diputación Floral de Gipuzkoa		<u>Bayley Mental Development Index (MDI)</u>
• The University of Oviedo, the KUTXA – Caja Gipuzkoa San Sebastián		Both trimesters MUFcr • All: 2.67 (-3.46, 8.81) • No significant interaction by sex
• The city councils of Zumarraga, Urretxu, Legazpi, Azpeitia, Beasain and Azkoitia in Gipuzkoa		Week 12 MUFcr • All: 0.89 (-4.55, 6.32)
Author declaration of interest: no COI		

•

- No significant interaction by sex

Week 32 MUFcr

- All: 2.65 (-2.14, 7.45)
- No significant interaction by sex

McCarthy, verbal

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

McCarthy, performance

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

McCarthy, numeric

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

McCarthy, memory

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

McCarthy, general cognitive

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), stratified
by fluoridated and non-
fluoridated zone**

Bayley Mental Development
Index (MDI)

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

McCarthy, verbal

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

McCarthy, performance

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

McCarthy, numeric

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

McCarthy, memory

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:

McCarthy, general cognitive

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, boys only

- 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; boys only

- 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
	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	++	Study reported on source and intake of drinking water (tap

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	characterization?	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 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

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: <ul style="list-style-type: none"> • Original study Study design: <ul style="list-style-type: none"> • Cross-sectional study Country: <ul style="list-style-type: none"> • India Participants: <ul style="list-style-type: none"> • School children (12-13 years of age) residing in Dhand of Amer Tehsil, Mohanpura, or Muhana of Sanganer Tehsil. Sampling time frame: <ul style="list-style-type: none"> • September 2011 – 	Exposures: <u>Fluoride levels in</u> <ul style="list-style-type: none"> • Water • Urine Method of exposure assessment: <ul style="list-style-type: none"> • Water fluoride: Acquired from the Public Health Engineering Department • Urine fluoride: Selective Ion Electrode Technique Exposure level: <u>Water fluoride concentration by group</u> <ul style="list-style-type: none"> • Group A: 2 ppm • Group B: 5 ppm 	Outcome(s): <ul style="list-style-type: none"> • IQ Method of outcome ascertainment: <ul style="list-style-type: none"> • Raven's Colored Progressive Matrices intelligence test 	Statistical analysis: <ul style="list-style-type: none"> • One-way ANOVA test and paired t-test were used • Statistical significance at $p < 0.05$ Results: Correlation between IQ and urinary fluoride level <ul style="list-style-type: none"> • Group A: $r = -0.161$ $p = > 0.05$ • Group B: $r = -0.485$ $p = < 0.01$ • Group C: $r = -0.334$ $p = < 0.05$ 	<ul style="list-style-type: none"> • "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

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>October 2011</p> <p>Sample size:</p> <ul style="list-style-type: none"> • N = 90 <p>Sex N (%):</p> <ul style="list-style-type: none"> • NR <p>Exclusions:</p> <ul style="list-style-type: none"> • Those with history of head trauma or injury • Those with congenital or acquired neurological disorders • Those with psychological disorders <p>Source of funding / support:</p> <ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Group C: 2 – 5 ppm <p><u>Urinary fluoride concentration by group</u></p> <ul style="list-style-type: none"> • Group A: 1.60ppm • Group B: 6.82 ppm • Group C: 2.69 ppm 			<p>in IQ level” (p. 3)</p> <ul style="list-style-type: none"> • “The results indicated that there was a positive correlation between excess fluoride in drinking water and IQ.” (p. 1)

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Author declaration of interest:</p> <ul style="list-style-type: none"> • No COI 				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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
	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	++ "The total number of school children aged 12-13 years at

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	exclusion from analysis?	<p>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)."</p>
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 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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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 ^[10]

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: Brazil</p> <p>Participants: High school students aged 17–20 years</p> <p>Sampling time frame: January to September 2017</p> <p>Sample size: 660 (331 exposed and 329 unexposed to fluoridated water)</p> <p>Sex: N (%): Boys: 275 (41.7%)</p> <p>Exclusions: • Students who had lived</p>	<p>Exposures</p> <p><u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Drinking water <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Fluoride in water by a specific ion electrode (Orion Model 96–09) coupled to the ion analyzer (Orion Star A211, São Paulo, Brazil). <p>Exposure level(s):</p> <p><u>Fluoride levels in:</u></p> <ul style="list-style-type: none"> • Fluoridated water: 0.50 to 0.90 ppm 	<p>Outcome(s): Dental fluorosis</p> <p>Method of outcome ascertainment: Thylstrup and Fejerskov (TF) index</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Chi-square test • Student's t tests • Logistic regression <p>Results:</p> <p><u>Fluorosis prevalence and severity (n, %)</u></p> <p>Fluorosis absent</p> <ul style="list-style-type: none"> • Exposed: 195 (58.9%) • Unexposed: 260 (79.0%) <p>Very mild or mild fluorosis:</p> <ul style="list-style-type: none"> • Exposed: 96 (29.0%) • Unexposed: 55 (16.7%) <p>Moderate fluorosis:</p> <ul style="list-style-type: none"> • Exposed: 40 (12.1%) • Unexposed: 14 (4.3%) <p>P<0.001</p> <p><u>Multivariate logistic regression</u></p>	<ul style="list-style-type: none"> • “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
<p>in the study area <70% of their lives.</p> <p>• Students with a fixed orthodontic appliance or those with amelogenesis imperfecta</p> <p>Source of funding / support NR</p> <p>Author declaration of interest: NR</p>	<p>• Non-fluoridated water: <0.05 ppm</p>	<p>The intra and inter-examiner kappa indexes were 0.87 and 0.85 for dental fluorosis.</p>	<p>Very mild or mild fluorosis</p> <p>• Exposed: AOR [adjusted odds ratio] =2.26 (95% CI: 1.54–3.32)</p> <p>• Unexposed: reference</p> <p>• P<0.001</p> <p>Moderate fluorosis</p> <p>• Exposed: AOR=3.66 (95% CI: 1.93–6.95)</p> <p>• Unexposed: reference</p> <p>• P<0.001</p>	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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.

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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?	++ 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 Thylstrup 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 [11]

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional ["pre-post cross-sectional design with comparison group"]</p> <p>Country: Canada</p> <p>Participants: Children aged ~7 years (grade 2 schoolchildren)</p> <p>Sampling time frame: <ul style="list-style-type: none"> • 2018-2019 school year • Pre-cessation data (2004/2005 and 2009/2010 [Calgary only]), early post-cessation data (2013/2014) from </p>	<p>Routes of exposures: Water fluoridation</p> <p><u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Fingernails • Water (in water treatment plants) <p>Method of exposure assessment: <u>Water fluoridation status</u></p> <ul style="list-style-type: none"> • Never exposed to water fluoridation (Calgary) • Always exposed to water fluoridation (Edmonton) <p><u>Fluoride levels in</u></p>	<p>Outcome(s): Dental fluorosis</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 <p>Results:</p> <p><u>Fluorosis prevalence (95% CI),</u> %</p> <p>[Note: 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.]</p> <p>Years 2018-2019</p>	<ul style="list-style-type: none"> • "Although estimates of 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
<p>previous studies</p> <p>Sample size:</p> <p><u>2018-2019</u></p> <ul style="list-style-type: none"> • Calgary: 1620 • Edmonton: 1402 <p><u>2004-2005</u></p> <ul style="list-style-type: none"> • Calgary: 380 • Edmonton: 41,749 <p><u>2009-2010</u></p> <ul style="list-style-type: none"> • Calgary: 365 • Edmonton: -- <p><u>2013-2014</u></p> <ul style="list-style-type: none"> • Calgary: 2084 • Edmonton: 1749 <p><u>Fingernail clippings</u></p> <p><u>(2018/2019)</u></p> <ul style="list-style-type: none"> • Calgary: 34 • Edmonton: 31 <p>Sex: N (%):</p> <p>NR</p> <p>Exclusions:</p> <p>NR</p>	<ul style="list-style-type: none"> • Fingernails: Method of analysis not reported; reference to Whitford et al. 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 <p>Exposure level(s):</p> <p><u>Total fluoride in fingernails</u></p> <p>Mean (95% CI), µg/g</p>	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Tooth Surface Index of 	<p><u>Calgary (water fluoridation ceased in 2011)</u></p> <ul style="list-style-type: none"> • Crude: 8.3 (6.6-10.3)* • Adjusted: 7.7 (5.9-9.6)* • Subset: 6.2 (4.3-8.9)* <p><u>Edmonton (water fluoridation continues)</u></p> <ul style="list-style-type: none"> • Crude: 19.4 (16.3-22.9) • Adjusted: 18.3 (14.9-21.6) • Subset: 18.8 (14.4-24.2) <p>*Calgary vs. Edmonton: P<0.05</p> <p>Changes over time (crude estimates)</p> <p><u>Calgary (water fluoridation ceased in 2011)</u></p> <ul style="list-style-type: none"> • 2004-2005: 22.6 (18.8, 26.9) • 2009-2010: 29.1 (24.6, 34.1) • 2013-2014: 19.9 (17.8, 22.2) • 2018-2019: 8.3 (6.6-10.3) <p><u>Edmonton (water fluoridation continues)</u></p> <ul style="list-style-type: none"> • 2004-2005: 39.8 (37.0, 42.7) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding / support:</p> <ul style="list-style-type: none"> • Research grant from the Canadian 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) 	<ul style="list-style-type: none"> • Calgary: 1.1 (0.9 to 1.2) • Edmonton: 1.6 (1.3 to 1.8) <p>Median (inter-quartile range), µg/g</p> <ul style="list-style-type: none"> • Calgary: 1.0 (0.7 to 1.2) • Edmonton: 1.3 (1.3 to 1.5) <p>P<0.0001</p> <p><u>Fluoride in water: range (average, if available), µg/L</u>²⁶</p> <p>Calgary</p> <ul style="list-style-type: none"> • Bearspaw plant: 2005: 0.6-0.8 2006: 0.7-0.7 2007: 0.6-0.7 2008: 0.7-0.7 	<p>Fluorosis [TSIF] criteria.</p> <ul style="list-style-type: none"> • Dental fluorosis expressed as prevalence: % with TSIF score ≥1 based 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 	<ul style="list-style-type: none"> • 2009-2010: no data • 2013-2014: 14.1 (11.4, 17.4) • 2018-2019: 19.4 (16.3-22.9) <p><u>Coefficient (95% CI) for difference of changes: -0.1 [-0.2 to -0.1], P<0.001).</u></p>	

²⁶ 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
<ul style="list-style-type: none"> • Dr Weijjs was supported by a CIHR Health System Impact Fellowship, 2017-2020 (Award # 403867). 	2009: 0.7-0.7 2010: 0.7-0.7 <u>2011: 0.1-0.7</u> 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)			
Author declaration of interest: No COI	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)			
	<ul style="list-style-type: none"> • 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 <u>2011: 0.1-0.7</u> 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)			
	2019: 0.6-0.8 (0.7)			
	• EL Smith plant:			
	2005: 0.7-0.9 (0.8)			

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
	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		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	++ Participants selected using same criteria. Sampling time

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	appropriate comparison groups?	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 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	++ DF examined using Tooth Surface Index of Fluorosis

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	assessment?	
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 [\[12\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride levels in</u>	Outcome(s): Dental fluorosis	Statistical analysis: • Descriptive analysis	• “The risk of dental fluorosis was significantly higher in the areas showing more fluoride content in drinking water.”
Study design: Cross-sectional	• Groundwater			
Country: India				
Participants: Children aged 6-12 years	Method of exposure assessment:		Results: Dean’s fluorosis index (mean)	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sampling time frame: NR Sample size: 1262 Sex: N (%): Boys: 615 (48.7%) Exclusions: <ul style="list-style-type: none"> Children who were not continuous residents of the study area since birth Source of funding / support: <ul style="list-style-type: none"> None Author declaration of interest: No COI	Fluoride in water: Ion Selective Electrode Method using ION check 45 m. Exposure level(s): Fluoride in groundwater (ppm): 0.532–8.802	Method of outcome ascertainment: Dean’s Fluorosis Index	by level of groundwater fluoride: <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> r=0.922; p<0.01 	<ul style="list-style-type: none"> “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.”

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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
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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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 [\[13\]](#)

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride levels in</u>	Outcome(s): Dental fluorosis	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)	• "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
Study design: Cross-sectional	• Urine • Groundwater used for drinking	Non-verbal intelligence quotient (IQ)	• Linear regression (Backward stepwise)	
Country: Pakistan	Method of exposure assessment:		Results: Dental fluorosis	
Participants: Children aged 5-16 years				

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sampling time frame: NR</p> <p>Sample size: 148 (118 exposed; 30 controls)</p> <p>Sex: N (%): Boys: 112</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Non-permanent residents in the study area • Drinking water source other than groundwater <p>Source of funding / support: None</p> <p>Author declaration of interest: No COI</p>	<ul style="list-style-type: none"> • Urinary fluoride by fluoride ion-selective electrode (Hanna, Model HI-522). • Water fluoride: NR <p>Exposure level(s):</p> <p><u>Water fluoride (mg/L)</u></p> <ul style="list-style-type: none"> • 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 <p><u>Urinary fluoride (mg/L)</u></p> <ul style="list-style-type: none"> • 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 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Dental fluorosis: Dean's index • Non-verbal IQ: Wechsler scale of intelligence (WISC-IV) 	<p><u>Frequency and severity of dental fluorosis, n (%)</u></p> <p>Control group</p> <ul style="list-style-type: none"> • Normal: 28 (94.0) • Questionable: 2 (6.0) <p>Exposed group</p> <ul style="list-style-type: none"> • Normal: 0 • Questionable: 16 (13.55) • Very mild: 22 (18.65) • Mild: 21 (17.80) • Moderate: 25 (21.19) • Severe: 34 (28.81) <p><u>Correlation analysis</u></p> <p>Water fluoride and urinary fluoride: $r=0.224$; $p=0.006$</p> <p>Water fluoride and dental fluorosis: $r=0.380$; $p=0.000$</p> <p>Urinary fluoride and dental fluorosis: $r=0.721$; $p=0.000$</p> <p><u>Linear regression analysis</u></p> <p>Fluoride in urine as an</p>	<p>that variations in dental fluorosis and IQ levels were more significantly associated with F-exposure compared to As.”</p>

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>independent variable:</p> <ul style="list-style-type: none"> • $\beta=0.38$ (SE 0.03) [unstandardized] • $\beta=0.66$ [standardized]; $p=0.00$ <p>Other independent variables in the model: gender, family economic status, arsenic in urine.</p> <p>Model summary: $F = 49.00$; adjusted $R^2=0.57$; $p=0.000$</p> <p>Non-verbal intelligence quotient (IQ)</p> <p><u>IQ score</u></p> <p>Control group: 80.25–127.75; mean 100.93 (SD 13.1)</p> <p>Exposed group: 63.97–127.31; mean 97.26 (SD 15.39)</p> <p>$P=0.233$</p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>Correlation analysis</u></p> <p>Water fluoride and urinary fluoride: $r=0.224$; $p=0.006$</p> <p>Water fluoride and IQ score: $r=-0.034$; $p=0.683$</p> <p>Urinary fluoride and IQ score: $r=-0.655$; $p=0.000$</p> <p>Dental fluorosis and IQ score: $r=-0.552$; $p=0.000$</p> <p><u>Note:</u> Levels of fluoride significantly correlated with arsenic levels.</p> <p><u>Linear regression analysis</u></p> <p>Fluoride in urine as an independent variable:</p> <ul style="list-style-type: none"> • $\beta=-3.45$ (SE 0.50) [unstandardized] • $\beta=-0.60$ [standardized] • $P=0.00$ 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>Other independent variables in the model: age, gender, parental education, dental fluorosis.</p> <p>Model summary: $F = 29.64$; adjusted $R^2=0.49$; $p=0.000$</p> <p><u>Intelligence level vs mean (SD)</u> <u>water fluoride (WF), urinary fluoride (UF), water arsenic (WA) and urinary arsenic (UA)</u></p> <p>Superior (IQ score ≥ 130): no participants with this level</p> <p>Above average (IQ score 120-129)</p> <ul style="list-style-type: none"> • 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 <p>High Average (IQ score 111-</p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			119) <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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 Low average (IQ score 80-89) <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • WF: 4.92±3.46 mg/L • UF: 8.10±5.84 mg/L 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • 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	

Risk of bias assessment				
Bias domain	Criterion	Response		
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	
	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 ^[14]

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in:</u>	Outcome(s): • Dental fluorosis	Statistical analysis: • Pearson's correlation	• "Correlation between fluorosis status and fluoride level in drinking
Study design:	• Groundwater			

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Cross-sectional</p> <p>Country: Egypt</p> <p>Participants: 7-14 years old children with no tooth fillings or braces, who live in the same region since birth</p> <p>Sampling time frame: December 2020- March 2021</p> <p>Sample size: 202</p> <p>Sex: N (%): NR</p> <p>Exclusions:</p> <ul style="list-style-type: none"> Teeth covered with filling or braces Parents or children who refused to join the study. Ethical Consideration <p>Source of funding / support:</p>	<p>Method of exposure assessment:</p> <ul style="list-style-type: none"> Water analysis was conducted in the National Research Centre (method unreported). <p>Exposure level(s):</p> <ul style="list-style-type: none"> <u>Fluoride Levels in drinking water:</u> 7.5-9.5, mean 8mg/L 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> Modified Dean's Index 	<p>Results:</p> <ul style="list-style-type: none"> <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% 	<p>water was performed by using Pearson`s correlation coefficient and revealed strong, positive, significant correlation."</p> <ul style="list-style-type: none"> "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
<ul style="list-style-type: none"> • Self-funded <p>Author declaration of interest: No COI</p>				

Risk of bias assessment				
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>		
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)	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
Detection	Can we be confident in the exposure characterization?	+	Water analysis was conducted in the National Research Centre (method unreported).
	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^[15]

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride level in</u>	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
Study design: Cross-sectional	• Drinking water			
Country: Sri Lanka				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants: Children aged 15 years</p> <p>Sampling time frame: NR</p> <p>Sample size: 1040 [total] 989 [analytical]</p> <p>Sex: N (%): Boys: 45.2% of the total sample</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • 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 <p>Source of funding / support:</p>	<p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Fluoride content in water by spectrophotometry <p>Exposure level(s):</p> <ul style="list-style-type: none"> • Fluoride levels in water: 0.0-1.9 mg/L 	<p>Method of outcome ascertainment: Thylstrup and Ferjeskov (TF) index</p>	<p>Results:</p> <p><u>Prevalence of dental fluorosis</u></p> <ul style="list-style-type: none"> • TF score > 0: 51.7% • TF score > 1: 41.5% • TF score > 2: 20.5% <p><u>Prevalence of dental fluorosis by TF score</u></p> <ul style="list-style-type: none"> • TF0 [normal]: 48.3% • TF1: 10.2% • TF2: 20.9% • TF3: 11.8% • TF4: 5.9% • TF5: 2.3% • TF6: 0.5% <p><u>Association between fluoride level in drinking water and prevalence of dental fluorosis (TF score>0)</u></p> <ul style="list-style-type: none"> • Water fluoride <0.3 mg/L: 42.3% • Water fluoride 0.31-0.6 mg/L: 62.8% 	<p>fluoride content in the drinking water source.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Research Grant (RG/2016/84/D) from the University of Peradeniya Author declaration of interest: NR			<ul style="list-style-type: none"> 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				
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>		
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	
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	NA	Not applicable	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	study?	
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 Thyslrtrup 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-Omouh 2021 [\[16\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride level in</u> Drinking water samples from wells	Outcome(s): Dental fluorosis prevalence and severity	Statistical analysis: Statistical significance at p = 0.05	“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 endemic areas.” (p. 707 – 708)
Study design: Cross-sectional study	Method of exposure assessment: Fluoride-ion selective electrode coupled with ionalyzer	Method of outcome ascertainment: Dean’s index used to determine dental fluorosis severity	Results: Frequency (%) distribution of dental fluorosis by Dean’s Fluorosis Index in Kuraymah	
Country: Jordan			<u>Normal</u> • N = 10 / 141 (7.1%)	
Participants: • School children residing in Ruwaished (age 15.3 +/- 1.4 years) and Kuraymah (age 16.1 +/- 1.3 years)	Exposure level: Average fluoride level in water (ppm) <u>Ruwaished</u> • 1.38		<u>Very mild</u> • N = 13 / 141 (9.2%)	
Sampling time frame: NR	<u>Kuraymah</u> • 1.10		<u>Mild</u> • N = 21 / 141 (14.9%)	
			<u>Moderate</u> • N = 51 / 141 (36.2%)	
			<u>Severe</u>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size:</p> <ul style="list-style-type: none"> • Ruwashed: 100 • Kuraymah: 141 <p>Sex: N (%):</p> <ul style="list-style-type: none"> • Ruwashed: Men: 60 (60%) • Kuraymah: Men: 85 (39.7%) <p>Exclusions:</p> <p>NR</p> <p>Source of funding / support: NR</p> <p>Author declaration of</p>			<ul style="list-style-type: none"> • N = 46 / 141 (32.6) <p>Frequency (%) distribution of dental fluorosis by Dean's Fluorosis Index in Ruwashed</p> <p><u>Normal</u></p> <ul style="list-style-type: none"> • N = 0 / 100 (0%) <p><u>Very Mild</u></p> <ul style="list-style-type: none"> • N = 9 / 100 (9%) <p><u>Mild</u></p> <ul style="list-style-type: none"> • N = 19 / 100 (19%) <p><u>Moderate</u></p> <ul style="list-style-type: none"> • N = 22/100 (22%) <p><u>Severe</u></p> <ul style="list-style-type: none"> • N = 50 / 100 (50%) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
interest: No COI				

Risk of bias assessment				
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>		
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	N/A	Not applicable	

Risk of bias assessment			
	subjects blinded to the study group during the study?		
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 I901, 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
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the	++	None identified

Risk of bias assessment	
study protocol)?	

Ayele 2021 [\[17\]](#)

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) Country: Ethiopia	Exposures: <u>Fluoride levels in</u> Ground water (community wells) Method of exposure assessment: The ion-selective electrode (ISE) Exposure level:	Outcome(s): <ul style="list-style-type: none"> • Skeletal fluorosis • Joint pain • Neurological manifestations (headache, paresthesia, loss of appetite, constipation, and fatigue) Method of outcome ascertainment: A comprehensive physical examination with emphasis	Statistical analysis: <ul style="list-style-type: none"> • Descriptive analysis • Univariate analysis • Multivariable regression Results: <ul style="list-style-type: none"> • 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 drinking water and joint pain were independent predictors of

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants: Persons aged 10–70 years old, selected at random from those who lived and used water wells from 23 rural villages</p> <p>Sampling time frame: Two sampling periods (between 2018 and 2019)</p> <p>Sample size: 316</p> <p>Sex (N):</p>	<ul style="list-style-type: none"> • Mean concentration: 6.8 ± 4.3 mg/L • Range: 0.3–15.5 mg/L 	<p>on neurological examination, conducted by two certified neurologists</p>	<p>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].</p> <ul style="list-style-type: none"> • 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 	<p>fluorosis.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Men: 176 (55.7%)</p> <p>Exclusions:</p> <p>NR</p> <p>Source of funding / support:</p> <p>NIEHS's career development grant</p> <p>Author declaration of interest:</p> <p>No COI</p>			<p>symptom, respectively.</p> <ul style="list-style-type: none"> • The mean fluoride level was higher for those individuals who reported 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). 	

Risk of bias assessment

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 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

Risk of bias assessment			
			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?	++	<p>Yes, the outcome (skeletal fluorosis) was assessed using comprehensive physical examination by two certified neurologists. Outcome assessment methods and lack of blinding of outcome assessors would not appreciably bias results.</p> <p>-</p> <p>The outcome (multiple neurological symptoms) was assessed using face-to-face interviews by 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</p>

Risk of bias assessment				
				results.
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	++ Yes, the primary outcome (medical conditions grouped as neurological) were 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	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Exclusions: Demolition victims of Yinpu Natural Village</p> <p>Source of funding / support: NR</p> <p>Author declaration of interest: No COI</p>	<p><u>Fluoride range:</u> 0.05-0.76 mg/L</p> <ul style="list-style-type: none"> <u>Urinary Fluoride</u> 0.04 - 3.76 mg/L (Geometric Mean: 0.8 mg/L) <p>Upper limit of normal value is ≤1.60 mg/L.</p>	<ul style="list-style-type: none"> 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). 	<p>Severe:0</p> <ul style="list-style-type: none"> <u>Highest DF in Minhou County</u> <u>Detection rates/years:</u> 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	
	Were the research personnel and human subjects	N/A	Not applicable	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	blinded to the study group during the study?	
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross sectional</p> <p>Country: United States</p> <p>Participants: US children and adolescents 6–19 years old (NHANES survey)</p> <p>Sampling time frame: 2015-2016</p>	<p>Exposures:</p> <p><u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Drinking water • Serum <p>Method of exposure assessment:</p> <p><u>Water fluoride:</u></p> <p>Measured electrometrically using the ion-specific electrode (CDC, 2017a).</p> <p><u>Serum fluoride:</u></p> <p>Measured in duplicate using the same sample and the average of two results was employed</p>	<p>Outcome(s):</p> <p>Dental fluorosis</p> <p>Method of outcome ascertainment:</p> <p>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 Dental Examiners Procedures Manual, 2016).</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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. <p>Results:</p> <ul style="list-style-type: none"> • The rate of fluoride concentration in water above the recommended level of 0.7 mg/L was 25%, but the prevalence 	<p>“Even low level of water or plasma fluoride exposure was associated with increased risk of dental fluorosis.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 2098 children and adolescents</p> <p>Sex: Men: 1,054 (50.24%)</p> <p>Exclusions: Survey respondents with missing any of the fluoride measurements, dental fluorosis assessment or complete data for all covariates and outcomes.</p> <p>Source of funding / support:</p>	<p>(Centers for Disease Control and Prevention, 2017b).</p> <p>Exposure level:</p> <p><u>Water fluoride (mg/L):</u> <u>Mean (SD)</u></p> <p>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)</p> <p><u>Plasma fluoride (µmol/L):</u> <u>Mean (SD)</u></p> <p>All: 0.35 (0.22) Men: 0.36 (0.19) Women: 0.34 (0.25)</p>		<p>of dental fluorosis was 70%.</p> <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> ○ <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), $p < 0.001$ <p>The pattern of regression between plasma fluoride and dental fluorosis was similar.</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • 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). <p>Author declaration of interest: No COI</p>	Children: 0.38 (0.24) Adolescents: 0.32 (0.20)			

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>

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 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
	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).

Risk of bias assessment			
	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 appropriate and researchers adhered to the study protocol)?	++	None identified

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: China</p> <p>Participants: Children aged 7–12 years old</p> <p>Sampling time frame: 2017</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Urine <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Urinary fluoride (UF): the ion-selective electrode method (Shanghai Exactitude Instrument, Shanghai, China). <p>Exposure level: Urinary fluoride (mg/l)</p> <p>All: 1.45 ± 0.88 Boys: 1.43 ± 0.89 Girls: 1.48 ± 0.87 t/x²: 0.490</p>	<p>Outcome(s): Thyroid hormone dysfunction:</p> <ul style="list-style-type: none"> • Total triiodothyronine (TT3) • Total thyroxine (TT4) • Thyroid-stimulating hormone (TSH) • Tvol (thyroid volumes) <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Clinical examination conducted by skilled medical professionals • Serum TT3, TT4, TSH: radiation immunoassay using the auto biochemical analyzer 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Linear regression <p>Results:</p> <p>Tvol (cm³)</p> <ul style="list-style-type: none"> • All 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 	<ul style="list-style-type: none"> • “Fluoride exposure can elevate the Tvol of school-age children, especially in boys, and high levels of iodine may alleviate this effect to some extent” • 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 446</p> <p>Sex (N): Boys: 237 (53.1%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • 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) <p>Source of funding /</p>	P-value: 0.624	<p>(Cobas C501, Roche Diagnostics, Basel, Switzerland)</p> <ul style="list-style-type: none"> • The B-mode ultrasound was performed to assess thyroid volumes (Tvols). 	<p>TT4 (nmol/l)</p> <ul style="list-style-type: none"> • All β (95% CI): 1.44 (– 1.28, 4.16), p-value: 0.297 • Boys: 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 <p>TT3 (nmol/l)</p> <ul style="list-style-type: none"> • All β (95% CI): – 0.05 (– 0.10, 0.01), p-value: 0.087 • Boys β (95% CI): – 0.08 (– 0.17, 	<p>was significantly lower in boys than girls (P < 0.001)</p> <ul style="list-style-type: none"> • Tvols increased by 0.22 (95% CI: 0.14, 0.31) cm³ with each standard deviation increment of UF. • Tvols in boys were more susceptible to 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>support:</p> <ul style="list-style-type: none"> • National Natural Science Foundation of China • The Henan Department of Science and Technology, China • Zhengzhou University <p>Author declaration of interest: No COI</p>			<p>0.01), p-value: 0.072</p> <ul style="list-style-type: none"> • 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 <p>TSH (μIU/ml)</p> <ul style="list-style-type: none"> • 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 • Interaction-β (95% CI): - 0.11 (- 0.33, 0.12) • p-value: 0.363 	<p>concentrations at moderate urinary iodine levels (\leq 300 μg/l).</p>

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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
	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	++ Yes, exposure was measured in water (the ion-specific electrode test) and serum (the ion-specific

Risk of bias assessment			
	characterization?		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 appropriate and researchers adhered to the study protocol)?	++	None identified

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cohort study</p> <p>Country: Canada</p> <p>Participants: Mother-child pairs in the Maternal-Infant Research on Environmental Chemicals (MIREC) study</p> <p>Sampling time frame: 2008 to 2011</p>	<p>Exposures:</p> <p><u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Maternal urine (MUF): prenatal exposure • Children urine (CUF): Childhood exposure <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<p>Outcome(s):</p> <ul style="list-style-type: none"> • Intelligence at 3 to 4 years of age <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Assessed by trained research assistants using the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) • Specific outcome measures include: Performance IQ (PIQ), Verbal IQ (VIQ), and Full-Scale IQ (FSIQ) 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Generalized estimating equations (GEE) used to assess association of interest • Statistical significance at $\alpha = 0.05$ for two-tailed test • Pint: interaction between exposure timing and fluoride level was assessed • Adjusted covariates: maternal education, maternal race, total HOME score, age at urine sampling, and prenatal second-hand smoke <p>Results:</p> <p>Change (95% CI) in age-</p>	<p>“Our results suggest the associations of prenatal and postnatal fluoride exposure with cognitive development may be modified by sex, 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)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 596</p> <p>Sex N (%): Female: 305 (51.2%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Fetal abnormalities • Medical complications • Gestational illicit drug use <p>Source of funding / support:</p> <ul style="list-style-type: none"> • National Institute of Environmental Sciences (NIEHS) • Chemicals Management Plan at 	<ul style="list-style-type: none"> • Infant fluoride intake (IFI) estimated over first year of life using water fluoride level and formula-feeding duration <p>Exposure level:</p> <p>Median (range) fluoride levels</p> <p><u>MUF T1 (mg/L)</u></p> <ul style="list-style-type: none"> • 0.31 (0.01 – 4.29) <p><u>MUF T2 (mg/L)</u></p> <ul style="list-style-type: none"> • 0.37 (0.03 – 5.28) <p><u>MUF T3 (mg/L)</u></p> <ul style="list-style-type: none"> • 0.49 (0.08 – 5.56) <p><u>IFI (mg F)</u></p> <ul style="list-style-type: none"> • 0.09 (0.00 – 0.61) <p><u>CUF (mg/L)</u></p> <ul style="list-style-type: none"> • 0.39 (0.05, 2.89) 		<p>normed in FSIQ scores per unit increase in standardized fluoride exposure</p> <p><u>Males</u></p> <ul style="list-style-type: none"> • MUF: -1.86 (-3.22, -0.49) • IFI: -0.01 (-1.67, 1.65) • CUF: 0.07 (-1.66, 1.80) • Pint: .012 <p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: -0.23 (-2.06, 1.60) • IFI: -0.72 (-2.34, 0.89) • CUF: -0.41 (-2.07, 1.24) • Pint: 0.77 <p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: -1.28 (-2.37, -0.18) • IFI: -0.38 (-1.53, 0.78) • CUF: -0.18 (-1.38, 1.02) • Pint: -0.23 <p>Change (95% CI) in age-normed in PIQ scores per unit increase in standardized</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Health Canada, the Ontario Ministry of the Environment, and the Canadian Institutes for Health Research			fluoride exposure	
Author declaration of interest:			<u>Males</u>	
No COI			<ul style="list-style-type: none"> • MUF: -3.01 • IFI: -1.45 (-3.40, 0.49) • CUF: -1.49 (-3.50, 0.53) • Pint: 0.01 	
			<u>Females</u>	
			<ul style="list-style-type: none"> • 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>	
			<ul style="list-style-type: none"> • 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>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • MUF: -0.25 (-1.57, 1.07) • IFI: 1.22 (-0.39, 2.83) • CUF: 1.61 (-0.06, 3.29) • Pint: 0.12 <p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: 0.87 (-0.91, 2.64) • IFI: 1.31 (-0.25, 2.87) • CUF: 0.63 (-0.98, 2.23) • Pint: 0.30 <p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: 0.15 (-0.91, 1.20) • IFI: 1.27 (0.15, 2.39) • CUF: 1.10 (-0.06, 2.26) • Pint: 0.04 <p>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</p> <p><u>Males</u></p> <ul style="list-style-type: none"> • MUF: -2.48 (-4.30, -0.66) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • IFI: -0.01 (-1.25, 1.24) • CUF: 0.09 (-2.10, 2.28) • Pint: 0.12 <p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: -0.31 (-2.76, 2.14) • IFI: -0.54 (-1.75, 0.66) • CUF: -0.52 (-2.62, 1.58) • Pint: 0.77 <p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: -1.71 (-3.17, -0.24) • IFI: -0.28 (-1.15, 0.58) • CUF: -0.23 (-1.75, 1.29) • Pint: 0.23 <p>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</p> <p><u>Males</u></p> <ul style="list-style-type: none"> • MUF: -4.02 (-6.15, -1.89) • IFI: -1.09 (-2.54, 0.37) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • CUF: -1.89 (-4.44, 0.67) • Pint: 0.01 <p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: -1.58 (-4.43, 1.28) • IFI: -2.03 (-3.43, -0.63) • CUF: -1.94 (-4.37, 0.50) • Pint: 0.01 <p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: -3.15 (-4.85, -1.44) • IFI: -1.58 (-2.59, -0.57) • CUF: -1.91 (-3.68, -0.15) • Pint: <0.001 <p>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</p> <p><u>Males</u></p> <ul style="list-style-type: none"> • MUF: -0.34 (-2.10, 1.43) • IFI: 0.92 (-0.29, 2.12) • CUF: 2.05 (-0.08, 4.16) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • Pint: 0.12 <p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: 1.16 (-1.22, 3.53) • IFI: 0.98 (-0.19, 2.15) • CUF: 0.79 (-1.24, 2.82) • Pint: 0.30 <p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: 0.20 (-1.22, 1.61) • IFI: 0.95 (0.11, 1.79) • CUF: 1.39 (-0.08, 2.86) • Pint: 0.04 <p>Sensitivity analysis where influential mother-child dyads were removed was conducted</p> <ul style="list-style-type: none"> • Association of MUF and FSIQ in boys became weaker and not statistically significant • No change in status of statistical significance for 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
other associations tested				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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 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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	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 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; Canadian norms; Wechsler, 2002). Outcomes included Performance IQ

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
		(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
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 [\[22\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride levels in</u>	Outcome(s): Dental fluorosis	Statistical analysis: • Chi-square test • Fisher's exact test	• The authors pointed to the high prevalence of dental fluorosis among children
Study design: Cross-sectional	• Water collected from school water			
Country: Brazil	fountains			

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants: Children aged 6-12 years</p> <p>Sampling time frame: April-September 2019</p> <p>Sample size: 610</p> <p>Sex: N (%): Boys: 329 (53.9%)</p> <p>Exclusions: • Children who used a fixed orthodontic appliance or had reading difficulties, tooth malformation (such as amelogenesis imperfecta, dentinogenesis imperfecta, or dentinal</p>	<p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Water fluoride: combined ion-specific fluoride electrode (ORION—9409BN) and a reference electrode (900200) connected to an ion analyser 710 A (ORION) <p>Exposure level(s): Water fluoride (ppm): 0.06-1.98</p> <p>Group I (≤ 0.7): 485 children</p> <p>Group II (> 0.7): 125 children, including:</p> <ul style="list-style-type: none"> • 0.7-1.0: 111 children • > 1.0-1.98: 14 children 	<p>Method of outcome ascertainment: Thysltrup and Fejerskov criteria</p>	<p>Results:</p> <p>Group I (water fluoride ≤ 0.7 ppm):</p> <ul style="list-style-type: none"> • Fluorosis absent: 306 (63.1%) children. • Fluorosis present: 179 (36.9%) children <p>Group II (water fluoride > 0.7 ppm):</p> <ul style="list-style-type: none"> • Fluorosis absent: 69 (55.2%) children. • Fluorosis present: 56 (44.8%) children <p>P=0.10</p> <p>Fluorosis absent: OR=1.02 (95% CI: 0.983-1.168)</p> <p>Fluorosis present: 0.77 (0.565-1.055)</p>	<p>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”.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
dysplasia)				
Source of funding / support:				
• NR				
Author declaration of interest: No COI				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	NA Not applicable

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	study?	
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)
	Can we be confident in the outcome assessment?	++ DF examined using the Thylstrup 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cohort study [clinical sub-cohort of The Swedish Mammography Cohort (SMC)]</p> <p>Country: Sweden</p> <p>Participants: All SMC participants who were <85 years of age and residing in the city of Uppsala or nearby</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Water • Diet • Urine <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<p>Outcome(s): Bone mineral density and fracture incidence in postmenopausal women</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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) 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Spearman’s rank correlational (rho). • Multivariable linear regression. <p>Results:</p> <ul style="list-style-type: none"> • At baseline: <ul style="list-style-type: none"> ○ Mean urinary fluoride: 1.2 mg/g creatinine (± 1.9) ○ mean dietary intake was 2:2 mg/d (± 0.9) • During follow-up: <ul style="list-style-type: none"> ○ 850, 529, and 187 cases of any fractures, osteoporotic fractures, and hip fractures, respectively, were 	<p>“In this cohort of postmenopausal women, the risk of fractures was 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”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>surrounding areas</p> <p>Sampling time frame: Baseline: 2004-2009 Follow-up: 2017</p> <p>Sample size: 4,306</p> <p>Sex (N): Women only (100%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Women who completed a short version of the FFQ • With incomplete FFQ data 	<ul style="list-style-type: none"> • Tea: scientific literature), • Urine: ion-selective electrode (Combined ISE F 800 DIN; WTW; Xylem Analytics Germany GmbH)). <p>Exposure level:</p> <ul style="list-style-type: none"> • 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). 		<p>ascertained.</p> <ul style="list-style-type: none"> • 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 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 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • 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 <p>Source of funding / support:</p> <ul style="list-style-type: none"> • Formas, the Swedish Research Council for 			<p>women with consistent long-term drinking water exposures prior to baseline strengthened associations between fractures and urinary fluoride.</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Environment • Agricultural Sciences and Spatial Planning • Swedish Research Council Author declaration of interest: No COI				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	++ Yes, participants were identified using the same method of ascertainment, recruited within the same

Risk of bias assessment			
	appropriate comparison groups?		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, 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 (>3SD above or below the log-transformed mean), without data on dietary fluoride, urine for element analysis, urinary creatinine, or DXA scans on

Risk of bias assessment		
		either side, with urine creatinine concentrations <0.3 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	Were all measured outcomes reported?	++ Yes, primary outcome (bone mineral density and

Risk of bias assessment				
reporting				bone fractures) 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

James 2021 [\[24\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Community water fluoridation (CWF)	Outcome(s): Dental fluorosis	Statistical analysis: • Association of interest was assessed using multivariate logistic regression	“In 2017, fluorosis prevalence was 18% in Dublin (full CWF) and 12% in Cork-Kerry (full CWF). Fluorosis was predominantly “very mild” with no
Study design: Before-and-after study	Method of exposure assessment: <u>Exposure group</u>	Method of outcome ascertainment: • Examinations were completed at school by	• Model adjusted for the following covariates: age,	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: Ireland</p> <p>Participants: Children (7 to 9 years of age) from Dublin and Cork-Kerry in the year 2002 and 2017</p> <p>Sampling time frame: 2002 and 2014</p> <p>Sample size (N): <u>Year 2000</u> • Dublin = 679 • Cork-Kerry = 565 <u>Year 2017</u> • Dublin = 707 • Cork-Kerry = 1,148</p>	<p><u>categories:</u></p> <ul style="list-style-type: none"> • Full CWF: lifetime exposure • No CWF: no exposure • Part CWF: sporadic exposure • Unknown: unknown CWF exposure <p>Exposure level: CWF before and after introduction of policy measures</p> <p><u>Before in 2002:</u></p> <ul style="list-style-type: none"> • 0.8 to 1.0 ppm <p><u>After in 2007:</u></p> <ul style="list-style-type: none"> • 0.6 to 0.8 ppm 	<p>dental examiners and nurses; this was performed from Jan to Jun 2002 and from Nov 2016 to May 2017</p> <ul style="list-style-type: none"> • 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 	<p>gender, ownership of medical card, and age of first toothpaste use</p> <p>Results: Odds (95% CI) of fluorosis prevalence in the year 2017 compared to 2002</p> <p><u>Dublin Full CWF</u></p> <ul style="list-style-type: none"> • OR = 16 (-13, 56); p = 0.312 <p><u>Cork-Kerry Full CWF</u></p> <ul style="list-style-type: none"> • OR = -7 (-41, 48); p = 0.771 <p><u>Cork-Kerry No CWF</u></p> <ul style="list-style-type: none"> • OR = 97 (-18, 373); p = 0.129 <p>"Among children with full</p>	<p>statistically significant difference between 2017 and 2002." (p. 507)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sex N (%): (2002)</p> <ul style="list-style-type: none"> • Dublin Full CWF Men: 360 (53%) • Cork-Kerry Full CWF Men: 149 (45%) • Cork-Kerry No CWF Men: 103 (44%) <p>(2017)</p> <ul style="list-style-type: none"> • Dublin Full CWF Men: 324 (46%) • Cork-Kerry Full CWF Men: 178 (47%) • Cork-Kerry No CWF Men: 380 (49%) <p>Exclusions: NR</p>			<p>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..."</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding / support:</p> <ul style="list-style-type: none"> • Health Research Board • Department of Health and the National Oral Health Office of the Health Services Executive <p>Author declaration of interest:</p> <ul style="list-style-type: none"> • No COI 				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
Selection	Was administered dose or exposure level	N/A Not applicable

Risk of bias assessment		
	adequately randomized?	
	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)
Detection	Can we be confident in the exposure characterization?	++ Yes, fluoride exposure levels were obtained from public water supply records

Risk of bias assessment			
	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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: India</p> <p>Participants: Residents with no evidence of skeletal fluorosis</p> <p>Sampling time frame:</p>	<p>Exposures: <u>Fluoride levels in</u> Ground water</p> <p>Method of exposure assessment: Data from the Groundwater Survey and Development Agency (GSDA)</p> <p>Exposure level:</p> <ul style="list-style-type: none"> • ≤1mg/L • 1.01-2.0 mg/L • 2.01-4.0 mg/L 	<p>Outcome(s): Skeletal fluorosis</p> <p>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.</p>	<p>Statistical analysis: Descriptive analysis</p> <p>Results: Relation of skeletal fluorosis with F- level in drinking water</p> <ul style="list-style-type: none"> • Normal (74.8%): <ul style="list-style-type: none"> ○ ≤1 ppm: 29.73% ○ 1.01–2.00: 28.14% ○ 2.01–4.00: 24.21% ○ >4.00: 17.92% • Mild (13.2%): <ul style="list-style-type: none"> ○ ≤1 ppm: 13.9% ○ 1.01–2.00: 16.47% ○ 2.01–4.00: 22.7% ○ >4.00: 46.87% • Moderate (6.0%): <ul style="list-style-type: none"> ○ ≤1 ppm: – ○ 1.01–2.00: 18.46% 	<ul style="list-style-type: none"> • “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
NR	<ul style="list-style-type: none"> • >4.0 mg/L 		<ul style="list-style-type: none"> ○ 2.01–4.00: 25.13% ○ >4.00: 56.41% • Severe (4.1%): <ul style="list-style-type: none"> ○ ≤1 ppm: – ○ 1.01–2.00: 15.55% ○ 2.01–4.00: 31.11% ○ >4.00: 53.34% • Very severe (1.9%): <ul style="list-style-type: none"> ○ ≤1 ppm: – ○ 1.01–2.00: 17.74% ○ 2.01–4.00: 25.81% ○ > 4.00: 56.45% 	
<p>Sample size: 3,268</p> <p>Sex (N): Men: 1,760 (53.86%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Radiological evidence of skeletal fluorosis • Social reasons • Lack of availability of time <p>Source of funding / support:</p>				

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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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

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?	+	Study provided some reasons for exclusion of participants (social reasons, lack of availability of time)
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	Were all measured outcomes reported?	++	Yes, primary outcome (skeletal fluorosis) discussed

Risk of bias assessment				
reporting				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

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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Drinking water • Urine	Outcome(s): • Genotoxicity (5-methylcytosine (5-mC) level)	Statistical analysis: • Statistical significance at $p \leq 0.05$	“...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
Study design: Cross-sectional study	Method of exposure assessment:	Method of outcome ascertainment: • Extraction and	Results: Mean (SD) of 5-mC by water quartile groups in mg/L	
Country:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>China</p> <p>Participants:</p> <p>Adults (> 18 years of age) born in one of five villages (Hongguang, Xiaoshan, Fushan, Wanfa, and Leye)</p> <p>Sampling time frame:</p> <p>April – September 2016</p> <p>Sample size:</p> <p>281</p>	<ul style="list-style-type: none"> • F-ion selective electrode <p>Exposure level:</p> <p>Fluoride quartiles in drinking water:</p> <ul style="list-style-type: none"> • Q1 (\leq P25): 1.4559 mg/L • Q2 (P25 ~ P50): 1.4559 ~ 2.2434 mg/L • Q3 (P50 ~ P75): 2.2434 ~ 3.2342 mg/L • Q4 ($>$P75): 3.2342 mg/L <p>Median levels of fluoride in drinking water</p>	<p>purification of genome</p> <p>DNA from blood: Universal cylindrical genomic DNA extraction kit</p> <ul style="list-style-type: none"> • Measured 5-mC level: Methyl Flash TM Global DNA Methylation ELISA Kit 	<ul style="list-style-type: none"> • Q1: 0.15 (0.09) • Q2: 0.11 (0.08) • Q3: 0.11 (0.08) • Q4: 0.14 (0.07) • $p = 0.001$ <p>Association between fluoride and 5-mC with cubic curve fitted</p> <ul style="list-style-type: none"> • $R^2 = 0.061$ • $F = 6.045$ • $p = 0.001$ 	<p>the disruption of DNA methylation in mammals may has a certain association with fluoride in natural exposures.” (p. 5 – 6)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sex (N): Men: 90 (32%) Exclusions: NR Source of funding / support: <ul style="list-style-type: none"> • National Natural Science Foundation of China • The Wu Liande Science Foundation of Harbin Medical University • Post-doctoral Scientific Research Developmental Fund of Heilongjiang Province 	<ul style="list-style-type: none"> • 2.2434 mg/L P50 (P25, P75) levels of fluoride in water by quartile (mg/L) <u>Q1 (N = 70)</u> <ul style="list-style-type: none"> • 1.100 (0.767, 1.414) <u>Q2 (N = 71)</u> <ul style="list-style-type: none"> • 1.853 (1.629, 2.069) <u>Q3 (N = 70)</u> <ul style="list-style-type: none"> • 2.691 (2.400, 2.949) <u>Q4 (N = 70)</u> <ul style="list-style-type: none"> • 4.123 (3.600, 5.200) P50 (P25, P75) levels of fluoride in urine by quartile (mg/L) <u>Q1 (N = 70)</u>			

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
	• 2.040 (1.612, 3.331)			
Author declaration of interest:	<u>Q2 (N = 71)</u>			
No COI	• 2.432 (1.981, 3.083)			
	<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		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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.

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?	-	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

Risk of bias assessment				
				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

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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross sectional study Country: Malaysia	Exposures: Fluoride levels in public drinking water supply Method of exposure assessment: Water fluoride: State	Outcome(s): Dental fluorosis Method of outcome ascertainment: <ul style="list-style-type: none"> Assessment of dental fluorosis was conducted by trained clinical and calibrated examiners (NAMN). 	Statistical analysis: <ul style="list-style-type: none"> Chi-squared analyses Logistic regression Results: <ul style="list-style-type: none"> “Fluorosis prevalence was lower (31.9 percent) among the younger children born after the reduction of fluoride 	<ul style="list-style-type: none"> “Fluorosis was lower among children born after the adjustment of fluoride concentration in the water.” “Fluoridated water remained as a strong risk factor

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants: Lifelong residents aged 9- and 12-year-olds</p> <p>Sampling time frame: 2015 (calculated using the following information reported by the authors)</p> <ul style="list-style-type: none"> • 9-year-old children (born between 1 January and 31 December 2006) • 12-year-old children (born 	<p>and national water quality reports</p> <p>Exposure level:</p> <ul style="list-style-type: none"> • Original: 0.7 ppm • Reduced: 0.5 ppm 	<ul style="list-style-type: none"> • 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. 	<p>concentration in the water, compared to a prevalence of (38.4 percent) in the older cohort.”</p> <p>Simple logistic regression of fluorosis and infant feeding (n=830)</p> <p><i>Fluorosis (Deans \geq 2), Type of water used to prepare formula</i></p> <p><u>Bottled water</u></p> <ul style="list-style-type: none"> • Fluorosis: 3 (9.4%) • No fluorosis: 29 (90.6%) • Reference <p><u>Tap water</u></p> <ul style="list-style-type: none"> • Fluorosis: 162 (25.7) • No fluorosis: 469 (74.3) • OR (95% CI): 3.34 (1.0–11.11) • P-value: 0.049* 	<p>for fluorosis after downward adjustment of its fluoride concentration.”</p> <ul style="list-style-type: none"> • “Early tooth brushing practices and fluoridated toothpaste were not statistically associated with fluorosis status.” <p>“However, the prevalence of fluorosis was significantly associated with parents' education level, parents' income, fluoridated water, type of infant feeding method, age</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>between 1 January and 31 December 2003)</p> <p>Sample size:</p> <p>1143 children aged 9-12 years old</p> <p>Sex: Boys: 491 (43%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Children who missed clinical examination. • Children with unerupted, partially unerupted or fractured 			<p><u>Filtered tap water</u></p> <ul style="list-style-type: none"> • Fluorosis: 47 (28.1%) • No fluorosis: 120 (71.9%) • OR (95% CI): 3.79 (1.1–13.03) • P-value: 0.035* <p>Simple logistic regression of fluorosis and water fluoride (n=1,143)</p> <p><i>Fluorosis (Deans \geq 2),</i></p> <p><u>0 lifetime</u></p> <ul style="list-style-type: none"> • Fluorosis: 30 (12.30%) • No fluorosis: 517 (57.4%) • Reference <p><u>0.5 ppm lifetime</u></p> <ul style="list-style-type: none"> • Fluorosis: 100 (41.2%) • No fluorosis: 204 (22.7%) • OR (95% CI): 8.45 (5.45–13.10) • P-value: 0.001 	<p>breast feeding ceased, use of formula milk, duration of formula milk intake, and type of water used to reconstitute formula milk”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>incisor(s), or have a fixed orthodontic appliance.</p> <p>Source of funding / support:</p> <p>Ministry of Higher Education, Malaysia</p> <p>Author declaration of interest:</p> <p>No COI</p>			<p><u>0.7 ppm for first 2 years and then 0.5 ppm</u></p> <ul style="list-style-type: none"> • Fluorosis: 113 (46.5%) • No fluorosis: 179 (19.9%) • OR (95% CI): 10.88 (7.03–16.84) • P-value: 0.001 <p>Multiple logistic regression of fluorosis (n=830)</p> <p><i>Fluorosis (Deans ≥ 2),</i></p> <p><i>Type of water used to prepare formula</i></p> <p><u>Bottled water</u></p> <ul style="list-style-type: none"> • Reference <p><u>Tap water</u></p> <ul style="list-style-type: none"> • OR (95% CI): 9.90 (1.28–76.38) • P-value: 0.028 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>Filtered tap water</u></p> <ul style="list-style-type: none"> • OR (95% CI): 8.78 (1.11–69.71) 0.040 • P-value: 0.040 <p>Multiple logistic regression of fluorosis and water fluoride (n=1,143)</p> <p><u>0 lifetime</u></p> <ul style="list-style-type: none"> • Reference <p><u>0.5 ppm lifetime</u></p> <ul style="list-style-type: none"> • Adjusted OR (95% CI): 5.97 (3.32–10.72) • P-value: <0.001 <p><u>0.7 ppm for first 2 years and then 0.5 ppm</u></p> <ul style="list-style-type: none"> • Adjusted OR (95% CI): 9.12 (5.15–16.14) • P-value: <0.001 	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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	++	Study provided reasons for exclusion of participants (children who missed clinical examination, those with

Risk of bias assessment			
	exclusion from analysis?		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 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride levels in</u>	Outcome(s): Dental fluorosis	Statistical analysis: <ul style="list-style-type: none"> • 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). 	<ul style="list-style-type: none"> • “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
Study design: Cross-sectional	<ul style="list-style-type: none"> • Groundwater used for household water supply. 		Results: <u>Prevalence of dental fluorosis (%) by subdistrict</u> <ul style="list-style-type: none"> • 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>	
Country: Thailand				
Participants: Children aged 6-10 years	Method of exposure assessment:			
Sampling time frame: 2015	<ul style="list-style-type: none"> • Annual records of fluoride concentrations in the groundwater used for the household water supply corresponding to the residence of each child from 2008 to 			
Sample size: 289				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>2015 were obtained from the database at Nakhon Pathom Provincial Public Health Office</p> <p>Sex: N (%): Boys: 153 (52.9%)</p> <p>Exclusions: Children who had not resided within the study area since birth</p> <p>Source of funding / support: Fogarty International Center of the National Institutes of Health under Award Number U2RTW010088.</p> <p>Author declaration of interest: No COI</p>	<p>2015 were obtained from the database at Nakhon Pathom Provincial Public Health Office</p> <p>Exposure level(s): Time-averaged fluoride concentration (ppm) by dental fluorosis status</p> <p><u>Normal (no fluorosis)</u></p> <ul style="list-style-type: none"> • Mean (SD): 2.0±1.6 • Median (IQR): 1.6 (1.1) • Range: 0.4-9.4 <p><u>Questionable fluorosis</u></p> <ul style="list-style-type: none"> • Mean (SD): 1.7±0.6 • Median (IQR): 1.7 (0.6) • Range: 0.6-3.0 <p><u>Very mild fluorosis</u></p> <ul style="list-style-type: none"> • Mean (SD): 2.8±2.2 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Children were examined by an “authorized dentist”. • Dean’s index was applied to classify the severity of dental fluorosis. 	<ul style="list-style-type: none"> • <0.7 ppm: 23.3% • 0.7–1.49 ppm: 37.7% • ≥1.5 ppm: 64.1% • Exact probability test; P < 0.001 <p><u>Severity of dental fluorosis by water fluoride level (number of cases; prevalence)</u></p> <ul style="list-style-type: none"> • <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 <p><u>PR (95% CI) by time-averaged water fluoride concentrations</u></p> <p>Univariable analysis</p>	<p>concentrations of < 0.7 ppm (the referent category) was evidence that reassured the safety of this recommended optimal fluoride level ...”</p> <ul style="list-style-type: none"> • “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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
	<ul style="list-style-type: none"> • Median (IQR): 2.0 (1.4) • Range: 0.4-9.4 <p><u>Mild fluorosis</u></p> <ul style="list-style-type: none"> • Mean (SD): 2.8±2.3 • Median (IQR): 2.1 (1.4) • Range: 1.1-9.4 <p><u>Moderate fluorosis</u></p> <ul style="list-style-type: none"> • Mean (SD): 4.1±3.5 • Median (IQR): 2.0 (7.1) • Range: 1.2-9.4 <p><u>All</u></p> <ul style="list-style-type: none"> • Mean (SD): 2.4±2.1 • Median (IQR): 1.9 (0.9) • Range: 0.4-9.4 <p>Time-averaged fluoride concentration (ppm) by subdistrict</p> <p><u>Sai Ngam</u></p>		<ul style="list-style-type: none"> • <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 <p>Multivariable analysis; adjusted for child’s demographic factors</p> <ul style="list-style-type: none"> • <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 <p>Multivariable analysis; adjusted for caregiver factors</p> <ul style="list-style-type: none"> • <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 <p>Multivariable analysis; adjusted for breastfeeding</p> <ul style="list-style-type: none"> • <0.7 ppm: reference 	<p>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-third of the children and 14.7% of the severity was beyond the very mild level.”</p> <ul style="list-style-type: none"> • “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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
	<ul style="list-style-type: none"> • Mean (SD): 3.72 (3.71) • Median (IQR): 1.40 (8.20) • Range: 0.39-9.38 		<ul style="list-style-type: none"> • 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 	in the reference group. The severity beyond the very mild level also grew to 15.7%.”
	<p><u>Bang Sai Pa</u></p> <ul style="list-style-type: none"> • Mean (SD): 3.06 (1.00) • Median (IQR): 3.35 (0.95) • Range: 1.07-3.94 		<p>Multivariable analysis; adjusted for oral health behaviors</p> <ul style="list-style-type: none"> • <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 	
	<p><u>Hin Mun</u></p> <ul style="list-style-type: none"> • Mean (SD): 2.31 (1.20) • Median (IQR): 1.97 (0.58) • Range: 1.13-5.94 		<p>Multivariable analysis; adjusted for all covariates</p> <ul style="list-style-type: none"> • <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 	
	<p><u>Bang Luang</u></p> <ul style="list-style-type: none"> • Mean (SD): 1.76 (0.36) • Median (IQR): 1.82 (0.51) 			

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
	<ul style="list-style-type: none"> • Range: 0.84-2.20 <p><u>Nin Phet</u></p> <ul style="list-style-type: none"> • Mean (SD): 0.44 (0.05) • Median (IQR): 0.46 (0.10) • Range: 0.37-0.51 			

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	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 participate
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: India</p> <p>Participants: Children (age 6 - 19 years) residing in 12 villages from the Rudraprayag District</p> <p>Sampling time frame: NR</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Ground water samples <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Samples from 3 water sources were randomly acquired per village • Ion-selective electrode <p>Exposure level:</p> <p><u>Low-risk area</u></p> <ul style="list-style-type: none"> • <0.6ppm <p><u>Intermediate risk area</u></p> <ul style="list-style-type: none"> • 0.6 – 1.5 ppm <p><u>High-risk area</u></p>	<p>Outcome(s): Dental fluorosis</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Determined using Deans Fluorosis Index 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Disease prevalence is presented as percentages by group <p>Results:</p> <p>Positive association between drinking water fluoride levels and dental fluorosis prevalence</p> <p>Percent of children with dental fluorosis by drinking water fluoride levels</p> <ul style="list-style-type: none"> • <0.7mg/L: 1% • > 1mg/L: 92% • p-value: <0.001 	<p>“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)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 558</p> <p>Sex: NR</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Not “residents of selected villages in their first 8 years of life” (p. 124) • Not “eldest child ... [from] each house” (p. 124) <p>Source of funding / support: Self</p>	>1.5ppm		<p>Prevalence of dental fluorosis by geological categories (fluoride level)</p> <p><u>Low-risk area (< 0.6ppm)</u></p> <ul style="list-style-type: none"> • No fluorosis <p><u>Intermediate risk area (0.6 – 1.5ppm)</u></p> <ul style="list-style-type: none"> • Dental fluorosis: 59.9% • Severe grade: 3.2% • Community fluorosis index: 1.05 <p><u>High-risk area (>1.5ppm)</u></p> <ul style="list-style-type: none"> • Dental fluorosis: 93% • Severe grade: 25.9% • Community fluorosis index: 2.59 	

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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	N/A Not applicable

Risk of bias assessment			
	study groups?		
	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)
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: Brazil</p> <p>Participants: 5 and 12 years old</p> <p>Sampling time frame: NR</p> <p>Sample size: 692 5 years old: 330 (47.6%) 12 years old: 362 (52.4%)</p> <p>Sex: N (%): Girls: 342 (49.4%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Use of fixed orthodontic appliance • Teeth with 	<p>Exposures:</p> <p><u>Fluoride levels in:</u></p> <ul style="list-style-type: none"> • Drinking water (water fountains of schools/ daycares) <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • <u>Fluoride levels in drinking water:</u> Ion Electrode Orion model No. 96-09, Orion Research Inc. coupled to Orion Star A214 Analyzer <p>Exposure level(s):</p> <p><u>Fluoridated Water (FW)</u> Conc:<0.05 µg/mL</p> <p><u>Non- Fluoridated</u></p>	<p>Outcome(s):</p> <ul style="list-style-type: none"> • Dental fluorosis <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Thylstrup-Fejerskov index (TF) 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Descriptive analysis • Logistic Regression <p>Results:</p> <p>Data for 12-year-old children [No dental fluorosis was observed in 5-year-old children in either group]</p> <ul style="list-style-type: none"> • <u>Dental Fluorosis in FW n(%)/NW n(%):</u> 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 <p>Kappa index: 0.90</p> <ul style="list-style-type: none"> • <u>Logistic regression Very mild/mild DF vs. FW (Desviance Test: p=0,088):</u> 	<p>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.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>amelogenesis imperfecta</p> <ul style="list-style-type: none"> • Not being born or raised in subjected area (Teresina) or not having access to public water supply. <p>Source of funding / support:</p> <ul style="list-style-type: none"> • Coordination of Improvement of Higher Education Personnel (Capes) <p>Author declaration of interest: No COI</p>	<p><u>Water (NFW)</u></p> <p>Conc: 0.5-0.6 µg/mL</p>		<p>OR:5.45</p> <p>CI 95%: 3.23-9.19</p> <p>P: <0.001</p> <p>Moderate DF vs. FW (Desviance Test: p=0,088):</p> <p>OR:11.11</p> <p>CI 95%: 4.43-27.87</p> <p>P: <0.001</p> <p>Reference: NFW for both Mild and moderate fluorosis</p> <p>Multiple analysis controlled by socioeconomic and demographics.</p>	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
			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
	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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: Ukraine</p> <p>Participants: Children aged 7–10 years old with clinically diagnosed fluorosis from endemic fluorosis areas (exposed to drinking water fluoride (> 1.5 ppm) for >5 years.)</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Drinking water <p>Method of exposure assessment: NR</p> <p>Exposure level: Drinking water: >1.5 ppm</p>	<p>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</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Dental fluorosis: Dean’s Fluorosis Index • Blood levels: X-ray fluorescence method 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Kolmogorov-Smirnov test • Kruskal-Wallis test • Spearman’s correlation analysis <p>Results:</p> <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • “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
<p>Sampling time frame:</p> <p>2014 (date of the project's ethics approval)</p> <p>Sample size:</p> <p>31</p> <p>Sex (N):</p> <p>Boys: 15 (48.4%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Known cardiac, lung, liver, kidney diseases or diabetes mellitus • Use of cardiac drugs • Consumption of any vitamin or mineral supplements for at least 2 weeks before blood 			<p>blood of children from the endemic fluorosis areas, compared with the values obtained in the blood of the healthy children from the non-fluorosis area</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>samples withdrawn</p> <p>Source of funding / support: NR</p> <p>Author declaration of interest: No COI</p>				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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?	<p style="text-align: center;">+</p> <p>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.</p>

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?	++	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)
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

Risk of bias assessment			
			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

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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposure: • Drinking <i>water fluoride</i> : 0.20–3.90 mg/L	Outcome(s): • IQ • Dental fluorosis	Statistical analysis: • Descriptive analysis • Multiple linear regression models	• “low-to-moderate fluoride exposure was associated with

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Cross-sectional Country: China Participants: 6.7–13 years old school children from Tianjin, China Sampling time frame: 2015 Sample size: 709 Sex: N (%): Girls: 328 (46.26%) Exclusions: NR	<ul style="list-style-type: none"> Urinary fluoride: 0.02–5.41 mg/L Urine creatinine: 0.30–2.99 mg/L Method of exposure assessment: <ul style="list-style-type: none"> 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 determination kit (Mindray, Shenzhen, 	(DF) Method of outcome ascertainment: <ul style="list-style-type: none"> 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. Dean's 	<ul style="list-style-type: none"> 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><i>IQ, Linear regression</i></u> <ul style="list-style-type: none"> Water fluoride (mg/L): IQ scores, β (95% CI) <ul style="list-style-type: none"> Q1 (≤ 0.30): Reference Q2 (0.30–1.00) <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> All: –2.77 (–5.44, –0.10) Boys: –4.45 (–8.41, –0.50) Girls: –1.72 (–5.91, 2.47) Q4 (> 1.60) <ul style="list-style-type: none"> All: –4.10 (–6.71, –1.48) 	the alteration of cholinergic system, DF and IQ” <ul style="list-style-type: none"> “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
<p>Source of funding / support:</p> <ul style="list-style-type: none"> 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) <p>Author declaration of interest:</p> <p>No COI</p>	<p>China)</p> <ul style="list-style-type: none"> Enzyme-linked immunosorbent assays (Shanghai Enzyme-linked Biotechnology, Shanghai, China) were used to detect the expression of cholinergic system. <p>Exposure level(s):</p> <ul style="list-style-type: none"> Normal fluoride-exposure group: water fluoride ≤ 1.0 mg/L High-fluoride-exposure group: water fluoride > 1.0 mg/L 	<p>classification system for dental fluorosis</p>	<p>Boys: -5.74 ($-9.57, -1.91$)</p> <p>Girls: -5.27 ($-9.32, -1.22$)</p> <ul style="list-style-type: none"> Urinary fluoride (mg/L): IQ scores, β (95% CI) <ul style="list-style-type: none"> Q1 (≤ 0.20): Reference Q2 (0.20–0.48) <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> All: -3.02 ($-5.71, -0.33$) Boys: -3.54 ($-7.60, 0.52$) Girls: -1.86 ($-6.01, 2.29$) Q4 (> 0.90) <ul style="list-style-type: none"> All: -4.49 ($-7.21, -1.77$) Boys: -6.09 ($-10.29, -1.90$) Girls: -5.98 ($-9.99, -1.96$) <p><u><i>IQ, Logistic regression</i></u></p> <ul style="list-style-type: none"> Water fluoride (mg/L) and IQ scores [OR (95% CI)] <ul style="list-style-type: none"> Superior and above (≥ 120): 0.69 (0.54, 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> 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)] <ul style="list-style-type: none"> ○ 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)] <ul style="list-style-type: none"> ○ Q1 (≤ 0.30): Reference ○ Q2 (0.30–1.00) <ul style="list-style-type: none"> Superior and above (≥ 120): 1.67 (0.92, 3.02) High normal (110-119): 1.22 (0.73, 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			2.04) 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)	
			<u>DF, Prevalence</u>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • Water fluoride (mg/L): dental fluorosis, PR (95% CI) <ul style="list-style-type: none"> ○ Q1 (≤ 0.30): Reference ○ Q2 (0.30–1.00) <ul style="list-style-type: none"> Crude: 1.21 (0.86, 1.70) Adjusted: 1.20 (0.85, 1.69) ○ Q3 (1.00–1.60) <ul style="list-style-type: none"> Crude: 3.78 (2.90, 4.94) Adjusted: 3.79 (2.90, 4.95) ○ Q4 (>1.60) <ul style="list-style-type: none"> Crude: 3.90 (3.00, 5.08) Adjusted: 3.97 (3.04, 5.17) • Urinary fluoride (mg/L): dental fluorosis, PR (95% CI) <ul style="list-style-type: none"> ○ Q1 (≤ 0.20): Reference ○ Q2 (0.20–0.48) <ul style="list-style-type: none"> Crude: 1.42 (1.09, 1.86) Adjusted: 1.66 (1.28, 2.14) ○ Q3 (0.48–0.90) <ul style="list-style-type: none"> 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)	
			<ul style="list-style-type: none"> Cholinergic system AChE (nmol/L) and DF/IQ [PR (95% CI)] <i>Either DF or IQ <120</i> <ul style="list-style-type: none"> Q1 (≤ 133.66): Reference Q2 (133.66–157.97) <ul style="list-style-type: none"> Crude: 1.09 (0.94,1.26) Adjusted: 1.06 (0.92,1.22) Q3 (157.97–184.03): <ul style="list-style-type: none"> Crude: 1.14 (1.00,1.31) Adjusted: 1.12 (0.97,1.28) Q4 (>184.03) <ul style="list-style-type: none"> Crude: 1.21 (1.06,1.38) Adjusted: 1.22 (1.07,1.38) <i>DF and IQ <120</i> <ul style="list-style-type: none"> Q1 (≤ 133.66): Reference Q2 (133.66–157.97) <ul style="list-style-type: none"> Crude: 1.29 (1.08,1.54) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>Adjusted: 1.27 (1.07,1.50)</p> <p>○ Q3 (157.97–184.03):</p> <p>Crude: 1.37 (1.16,1.62)</p> <p>Adjusted: 1.37 (1.17,1.62)</p> <p>○ Q4 (>184.03)</p> <p>Crude: 1.46 (1.25,1.72)</p> <p>Adjusted: 1.44 (1.23,1.68)</p> <p>• “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.”</p>	

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

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
	concealed? 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					
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>			
	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		

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: Indonesia</p> <p>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 disease, or were not undergoing treatment.</p> <p>Sampling time frame: NR</p>	<p>Exposure:</p> <ul style="list-style-type: none"> • Ground water <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • NR 	<p>Outcome(s):</p> <ul style="list-style-type: none"> • IQ • Dental fluorosis 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Univariate analysis • Bivariate analysis <p>Results:</p> <p>Dental fluorosis</p> <ul style="list-style-type: none"> • High-fluoride area: <ul style="list-style-type: none"> ○ 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%) 	<ul style="list-style-type: none"> • “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.”

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 100</p> <p>Sex: N (%): Females: 64 (64.0%)</p> <p>Exclusions: • NR</p> <p>Source of funding / support: • NR</p> <p>Author declaration of interest: • No COI</p>	<p>Exposure level(s):</p> <ul style="list-style-type: none"> • High fluoride area: 1.6 ppm • Low fluoride area: 0.10 ppm 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Dental fluorosis was assessed using Dean's fluorosis index • IQ was assessed using Raven's Color Progressive Matrix component. 	<ul style="list-style-type: none"> • Low-fluoride area: <ul style="list-style-type: none"> ○ 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%) <p>IQ</p> <ul style="list-style-type: none"> • High-fluoride area: <ul style="list-style-type: none"> ○ Low: 17 (28.3%) ○ High: 43 (71.7%) • Low-fluoride area: <ul style="list-style-type: none"> ○ Low: 0 (0%) ○ High: 40 (100%) <p>IQ and Dental fluorosis</p> <ul style="list-style-type: none"> • Dental fluorosis: <ul style="list-style-type: none"> ○ Low: 15 (37.5%) ○ High: 25 (62.5%) 	<ul style="list-style-type: none"> • "The level of intelligence of students who live in the high-fluorine area is lower than students who live in low fluorine area."

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • No dental fluorosis: <ul style="list-style-type: none"> ○ 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	-	NR	

Risk of bias assessment				
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>		
	characterization? 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	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: China</p> <p>Participants: School children aged 7 to 13 years old</p> <p>Sampling time frame: 2015</p> <p>Sample size: 952</p> <p>Sex: N (%): Girls: 481 (50.5%)</p>	<p>• Exposure: Fluoride content in</p> <p>• Drinking water</p> <p>• Urine</p> <p>• Hair and nail</p> <p>Method of exposure assessment:</p> <p>• Water samples were collected from each public supply in the villages.</p> <p>• Fluoride concentration was assessed using the national standardized ion-selective</p>	<p>Outcome(s):</p> <p>• IQ</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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. <p>Results:</p> <ul style="list-style-type: none"> • Water fluoride (mg/L) <ul style="list-style-type: none"> ○ High (IQ ≥ 120): 0.70 (0.40–1.00) ○ Non-high (70 ≤ IQ < 120): 1.00 (0.50–1.90) • Urinary fluoride (mg/L) <ul style="list-style-type: none"> ○ High (IQ ≥ 120): 0.33 (0.13–0.81) 	<ul style="list-style-type: none"> • “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
<p>Exclusions:</p> <ul style="list-style-type: none"> • 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). <p>Nails dyed or with nails samples less than 0.2 g (n = 340).</p>	<p>electrode method in China</p> <ul style="list-style-type: none"> • An early-morning spot urine sample was collected from each subject. • Hair samples were collected from the occipital zone of the scalp. 		<ul style="list-style-type: none"> ○ Non-high (70 ≤ IQ <120): 0.60 (0.16–2.22) <ul style="list-style-type: none"> • Hair fluoride (µg/g) <ul style="list-style-type: none"> ○ High (IQ ≥ 120): 8.26 (5.72–10.48) ○ Non-high (70 ≤ IQ <120): 14.39 (10.25–20.56) • Nail fluoride (µg/g) <ul style="list-style-type: none"> ○ High (IQ ≥ 120): 11.71 (8.53–14.64) ○ Non-high (70 ≤ IQ <120): 19.76 (14.16–27.32) <p><u>Fluoride exposure and high intelligence: OR (95% CI)</u></p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding / support:</p> <ul style="list-style-type: none"> • 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 <p>Author declaration of interest:</p> <p>No COI</p>	<p>Exposure level(s):</p> <ul style="list-style-type: none"> • Water fluoride (mg/L) <ul style="list-style-type: none"> ○ Tertile 1 (≤ 0.60) ○ Tertile 2 (0.61–1.40) ○ Tertile 3 (> 1.40) • Urinary fluoride (mg/L) <ul style="list-style-type: none"> ○ Tertile 1 (≤ 0.22) ○ Tertile 2 (0.23–1.80) ○ Tertile 3 (> 1.80) • Hair fluoride ($\mu\text{g/g}$) <ul style="list-style-type: none"> ○ Tertile 1 (≤ 10.40) ○ Tertile 2 (10.41–17.02) ○ Tertile 3 (> 17.02) • Nail fluoride ($\mu\text{g/g}$) 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Water fluoride (mg/L) <ul style="list-style-type: none"> ○ Tertile 1 (≤ 0.60) Reference ○ Tertile 2 (0.61–1.40) 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) <ul style="list-style-type: none"> ○ 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) Adjusted: 0.41 (0.26, 0.66) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
	<ul style="list-style-type: none"> ○ Tertile 1 (≤ 14.64) ○ Tertile 2 (14.65–23.41) ○ Tertile 3 (> 23.41) 		<ul style="list-style-type: none"> ● Hair fluoride ($\mu\text{g/g}$) <ul style="list-style-type: none"> ○ 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 ($\mu\text{g/g}$) <ul style="list-style-type: none"> ○ Tertile 1 (≤ 14.64) Reference ○ Tertile 2 (14.65–23.41) Crude: 0.15 (0.08, 0.29) 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) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>Does-response relationships of IQ scores with fluoride exposures</u></p> <ul style="list-style-type: none"> • 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 $\mu\text{g/g}$ increment of hair fluoride or nail fluoride. • Adjustment: age, sex, maternal education and paternal education. • Water fluoride (mg/L) <ul style="list-style-type: none"> ○ 0.20-3.40 <ul style="list-style-type: none"> Crude: -1.24 (-1.48, -0.99) Adjusted: -1.16 (-1.41, -0.91) ○ 3.40-3.90 <ul style="list-style-type: none"> Crude: -5.36 (-8.54, -2.18) Adjusted: -4.21 (-7.54, - 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			0.87) <ul style="list-style-type: none"> • Urinary fluoride (mg/L) <ul style="list-style-type: none"> ○ 0.01-1.60 <ul style="list-style-type: none"> Crude: 0.96 (0.29, 1.63) Adjusted: 1.01 (0.34, 1.68) ○ 1.60-2.50 <ul style="list-style-type: none"> Crude: -5.08 (-6.94, -3.22) Adjusted: -5.23 (-7.07, -3.39) ○ 2.50-5.54 <ul style="list-style-type: none"> Crude: -0.50 (-1.13, 0.14) Adjusted: -0.34 (-0.98, 0.30) • Hair fluoride (µg/g) <ul style="list-style-type: none"> ○ 3.23-10.50 <ul style="list-style-type: none"> Crude: -2.34 (-2.69, -1.99) Adjusted: -2.34 (-2.69, -1.99) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> ○ 10.50-45.04 <ul style="list-style-type: none"> Crude: -0.41 (-0.49, -0.34) Adjusted: -0.42 (-0.50, -0.34) • Nail fluoride (µg/g) <ul style="list-style-type: none"> ○ 2.08-14.50 <ul style="list-style-type: none"> Crude: -1.11 (-1.41, -0.81) Adjusted: -1.10 (-1.41, -0.80) ○ 14.50-99.60 <ul style="list-style-type: none"> Crude: -0.50 (-0.56, -0.44) Adjusted: -0.49 (-0.55, -0.43) <p><u>Interaction of SNP-set score with fluoride exposure on high intelligence OR (95% CI).</u></p> <ul style="list-style-type: none"> • <i>The P-value for interaction (p-inter) was adjusted for age, sex, maternal education and paternal education.</i> • <i>High SNP: -set score group (-</i> 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>1.59 to 0.00):</p> <ul style="list-style-type: none"> • Low SNP-set score group (-2.90 to -1.59): • Water fluoride (binary variable based on the limit of 1.00 mg/L) <ul style="list-style-type: none"> ○ 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) <ul style="list-style-type: none"> ○ 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 	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
			based on the median level of 14.00 µg/g <ul style="list-style-type: none"> ○ Sample size: 719 ○ High SNP: 0.17 (0.08, 0.34) ○ 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) <ul style="list-style-type: none"> ○ 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

<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>		<i>Response</i>
			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
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	++	Yes, fluoride exposure levels were obtained from drinking

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	characterization?	
	Can we be confident in the outcome assessment?	+
Selective reporting	Were all measured outcomes reported?	++
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++

water samples that were collected from the local source of water supply in each village. Fluoride concentration in water was assessed using the national standardized ion-selective electrode method in China.

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

Yes, the primary outcomes discussed in methods were presented in the results section with adequate level of detail for data extraction.

None identified.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: China</p> <p>Participants: children, aged 6–11 years old, from endemic and non-endemic fluorosis areas in Tianjin, China.</p> <p>Sampling time frame: 2018</p> <p>Sample size:</p>	<p>Exposure: Fluoride concentration in</p> <ul style="list-style-type: none"> • Drinking water • Urine <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Urinary fluoride: The national standardized method ion analyzer EA940 with F-ion selective electrode (Shanghai constant magnetic electronic technology Co, Ltd, China) 	<p>Outcome(s):</p> <ul style="list-style-type: none"> • IQ 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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). 	<ul style="list-style-type: none"> • “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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
567				effects of fluoride exposure on IQ; UF, ANKK1 Taq1A, COMT Val 158 Met and MAOA uVNTR have a high-dimensional interaction on IQ.”
<p>Sex: N (%): Girls: 283 (49.9%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Negative long-term residence • Mental retardation in an immediate family member • Missing IQ test, questionnaire or physical examination • No results of genotyping measurement <p>Source of funding / support: The National Natural Science Foundation of China (Grant No.</p>	<p>Exposure level(s):</p> <p>Fluoride in drinking water:</p> <ul style="list-style-type: none"> • High fluoride areas: 1.53–2.84 mg/L • Non-endemic fluorosis area (WF: 0.15–0.37 mg/L <p>Fluoride in urine:</p> <ul style="list-style-type: none"> • Urinary fluoride concentration was not normally distributed, with a median (quantile 1, quantile 3) of 1.03 (0.72, 1.47) mg/L • After log transformation, the 	<p>Method of outcome ascertainment:</p> <p>The Combined Raven’s Test (modified in China)</p>	<p>Results:</p> <p><u>Associations between UF and IQ scores</u></p> <ul style="list-style-type: none"> • Overall: Log_UF were inversely linear associated with IQ score ($P < 0.05$) in both crude model and adjusted model • β (95% CI): <ul style="list-style-type: none"> ○ 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; $p=0.006$) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
81573107, 81372934).	mean (\pm SD) Log_UF was 0.015 (\pm 0.252)			
Author declaration of interest:				
No COI				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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.
Performance	Were experimental conditions identical across study groups?	N/A Not applicable

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
	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.
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: USA</p> <p>Participants: US children and adolescents 6–19 years old (NHANES survey)</p>	<p>Exposures:</p> <p><u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Drinking water • Serum <p>Method of exposure assessment:</p> <p>Levels of fluoride in water and serum were tested using the ion-specific electrode method</p> <p>Exposure level:</p> <ul style="list-style-type: none"> • Water fluoride (mg/L) <ul style="list-style-type: none"> ○ Total: 0.36 (0.30, 0.42) 	<p>Outcome(s):</p> <p>Sex steroid hormones [testosterone, estradiol and sex hormone-binding globulin (SHBG)]</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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) <p>Results:</p> <ul style="list-style-type: none"> • Compared with subjects at the first tertile of plasma fluoride, percent changes (95% CI) in testosterone 	<p>“The data indicated 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.”</p>

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sampling time frame: 2013 – 2016</p> <p>Sample size: 3,392</p> <p>Sex (N): Males Total: 780 (50.6%) Children: 936 (50.6%) Adolescents: 1,716 (50.6%)</p> <p>Exclusions: Participants missing information on fluoride levels in plasma or water, sex steroid hormones of testosterone, estradiol, SHBG, or the examined</p>	<ul style="list-style-type: none"> ○ 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 <p>• Plasma fluoride (umol/L)</p> <ul style="list-style-type: none"> ○ Total: 0.35 (0.33, 0.37) ○ Male children: 0.38 (0.36, 0.41) ○ Male adolescents: 0.34 (0.32, 0.36) ○ Female children: 0.36 (0.34, 0.37) ○ Female adolescents: 0.33 (0.31, 0.35) 	<p>measurements of the reaction products</p>	<p>were:</p> <ul style="list-style-type: none"> ○ Second tertile: –8.08% (–17.36%, 2.25%) ○ Third tertile: –21.65% (–30.44%, –11.75%) ○ P trend <0.001 <p>• Male adolescents at the third tertile of plasma fluoride had decreased levels of testosterone: –21.09% (–36.61% to –1.77%).</p> <p>• Similar inverse associations were also found when investigating the relationships between plasma fluoride and estradiol.</p> <p>• Decreased levels of SHBG associated with water and plasma fluoride</p> <ul style="list-style-type: none"> ○ Male adolescents (third 	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>covariates.</p> <p>Source of funding / support:</p> <p>National Natural Science Foundation of China</p> <p>Author declaration of interest: No COI</p>	<ul style="list-style-type: none"> o p-value: <0.001 		<p>tertile): -9.39% (-17.25% to -0.78%)</p> <ul style="list-style-type: none"> o Female children (second tertile): -10.78% (-17.55% to -3.45%) <p>Percent change in testosterone (95% CI) at tertiles T2 and T3, compared to T1:</p> <p><u>Total</u></p> <ul style="list-style-type: none"> • T2: -7.95 (-20.47, 6.56) • T3: -8.11 (-15.84, 0.33) • p trend = 0.069 <p><u>Male Children</u></p> <ul style="list-style-type: none"> • T2: 10.90 (-8.11, 33.85) • T3: -7.56 (-21.80, 9.27) • p trend = 0.458 <p><u>Male Adolescents</u></p>	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • T2: -2.35 (-19.83, 18.94) • T3: -7.43 (-24.79, 13.94) • p trend = 0.461 <p><u>Female Children</u></p> <ul style="list-style-type: none"> • T2: -1.07 (-14.11, 13.96) • T3: -3.97 (-15.95, 9.72) • p trend = 0.549 <p><u>Female Adolescents</u></p> <ul style="list-style-type: none"> • T2: -2.08 (-11.75, 8.66) • T3: -3.58 (-14.75, 9.06) • p = trend 0.540 <p>Percent change in Estradiol (95% CI) at tertiles T2 and T3, compared to T1:</p> <p><u>Total</u></p> <ul style="list-style-type: none"> • T2: -4.55 (-16.08, 8.56) • T3: 1.48 (-6.97, 10.70) 	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
			• p trend = 0.896	
			<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	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>Percent change in SHBG (95% CI) at tertiles T2 and T3, compared to T1:</p> <p><u>Total</u></p> <ul style="list-style-type: none">• T2: 2.71 (-4.84, 10.86)• T3: -2.75 (-9.69, 4.74)• p = trend 0.557 <p><u>Male Children</u></p> <ul style="list-style-type: none">• T2: 5.38 (-2.14, 13.48)• T3: -4.14 (-10.65, 2.85)• p trend = 0.322 <p><u>Male Adolescents</u></p> <ul style="list-style-type: none">• T2: 0.38 (-7.95, 9.47)• T3: -9.39 (-17.25, -0.78)• p trend = 0.038 <p><u>Female Children</u></p> <ul style="list-style-type: none">• T2: -1.74 (-11.50, 9.10)• T3: 0.12 (-7.47, 8.34)• p trend = 0.984	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<u>Female Adolescents</u> <ul style="list-style-type: none"> • T2: 2.09 (-13.3, 19.98) • T3: -0.37 (-12.06, 12.88) • p trend = 0.996 	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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

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 (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 2020 [\[37\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Urine	Outcome(s): • IQ scores • Thyroid Stimulating Hormone (TSH) • Dopamine (DA)	Statistical analysis: • Descriptive statistics Results: Mean (\pm SD) IQ by urinary	Although fluoride was not the main focus ²⁷ , the study reported non-significant frequency differences between urinary
Study design: Cross-sectional study	Method of exposure			

²⁷ 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
Country: China Participants: School aged children (7 – 12 years) from Tianjin Sampling time frame: 2014 - 2018 Sample size: 498 Sex: Boys: 248 (49.8%)	assessment: <ul style="list-style-type: none"> Fluoride ion selective electrode method Exposure level: Distribution by urinary fluoride levels (N; %) <ul style="list-style-type: none"> <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: <ul style="list-style-type: none"> IQ: Combined Raven's Test (CRT) TSH: measured in serum using electrochemical luminescence method DA: measured in plasma using ELISA and DA kit 	fluoride levels <u>< 1.6 mg/L</u> <ul style="list-style-type: none"> 112.16 (±11.50) <u>1.6 – 2.5 mg/L</u> <ul style="list-style-type: none"> 112.05 (±12.01) <u>≥ 2.5 mg/L</u> <ul style="list-style-type: none"> 110.00 (±14.92) <u>p-value</u> <ul style="list-style-type: none"> 0.578 Median (q1-q3) TSH in uIU/mL by urinary fluoride levels <u>< 1.6 mg/L</u> <ul style="list-style-type: none"> 2.81 (2.21 – 3.81) <u>1.6 – 2.5 mg/L</u> <ul style="list-style-type: none"> 2.82 (2.01 – 3.82) 	fluoride levels and IQ scores, and TSH and DA levels

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Exclusions:			≥ 2.5 mg/L	
<ul style="list-style-type: none"> • Had incomplete information • Insufficient samples of blood 			<ul style="list-style-type: none"> • 3.29 (2.30 – 4.48) 	
Source of funding / support:			<u>p-value</u>	
<ul style="list-style-type: none"> • National Nature Science Foundation of China • Tianjin Health Inspection Fund 			<ul style="list-style-type: none"> • 0.287 	
Author declaration of interest:			Median (q1-q3) DA in ng/L by urinary fluoride levels	
No COI			< 1.6 mg/L	
			<ul style="list-style-type: none"> • 5.62 (3.08 – 12.15) 	
			<u>1.6 – 2.5 mg/L</u>	
			<ul style="list-style-type: none"> • 5.77 (3.01 – 12.59) 	
			≥ 2.5 mg/L	
			<ul style="list-style-type: none"> • 7.24 (2.16 – 15.23) 	
			<u>p-value</u>	
			0.925	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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
	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-

Risk of bias assessment								
		2015).						
	Can we be confident in the outcome assessment?	<table border="1"> <tr> <td style="background-color: #90EE90;">+</td> <td>IQ measured using Combined Raven's Test (CRT). Unclear blinding</td> <td style="background-color: #008000;">++</td> <td>TSH measured in serum using electrochemical luminescence method</td> <td style="background-color: #008000;">++</td> <td>DA measured in plasma using ELISA and DA kit</td> </tr> </table>	+	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
+	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?	<table border="1"> <tr> <td style="background-color: #008000;">++</td> <td>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</td> </tr> </table>	++	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				
++	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							
Other sources	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	<table border="1"> <tr> <td style="background-color: #008000;">++</td> <td>None identified</td> </tr> </table>	++	None identified				
++	None identified							

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: Saudi Arabia</p> <p>Participants: Dental college patients (aged 9 to 50 years)</p> <p>Sampling time frame: July – December 2019</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Water wells • Filtration plants • Commercial brand water bottles <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Collected samples (N= 63) from 12 regions/cities and 9 water bottle brands <p>Exposure level: Mean (SD) Fluoride levels in ppm by water source type</p>	<p>Outcome(s): Dental Fluorosis</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Assessments were completed by two dentists and two dental assistants • Severity was determined using Dean’s index 	<p>Statistical analysis: NR</p> <p>Results: Association between dental fluorosis and sources of drinking water</p> <p><u>Well Water</u></p> <ul style="list-style-type: none"> • None: 163 • Questionable: 141 • Very Mild: 105 • Mild: 71 • Moderate: 12 • Severe: 3 • Total: 495 <p><u>Filtered Water</u></p> <ul style="list-style-type: none"> • None: 414 • Questionable: 197 	<p>“The results revealed that fluoride levels varied between 0.03 and 3.8 ppm. People who drank well water 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</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sample size: 1,150 Sex N: Men: 609 (53%) Exclusions: Patients without primary or permanent teeth fully erupted Source of funding / support: Deanship of Scientific Research Author declaration of interest: No COI	<ul style="list-style-type: none"> • Well Water 1.97 (0.20) <ul style="list-style-type: none"> • Filtered Water 1.05 (0.69) <ul style="list-style-type: none"> • Bottled Water 1.09 (0.10)		<ul style="list-style-type: none"> • Very Mild: 36 • Mild: 5 • Moderate: 3 • Severe: 0 • Total: 665 <u>Total</u> <ul style="list-style-type: none"> • None: 577 • Questionable: 338 • Very Mild: 141 • Mild: 76 • Moderate: 15 • Severe: 3 • Total: 1150 <u>p-value</u> <ul style="list-style-type: none"> • <0.002 	water in the Asir region.”

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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

Risk of bias assessment			
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 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: Brazil</p> <p>Participants: Children (6 to 12 years of age) from rural public schools in São João do Rio do Peixe, Poço José de Moura, Marizópolis, and Uiraúna</p>	<p>Exposures: <u>Fluoride level in</u> • Water samples</p> <p>Method of exposure assessment: “Combined ion-specific fluoride electrode ... and a reference electrode ... connected to an ion analyser 710 A” (p. 476)</p> <p>Exposure level: Level of residual fluoride in water (ppm): Range: 0.06 – 1.98</p>	<p>Outcome(s): Dental fluorosis</p> <p>Method of outcome ascertainment: • Single examiner with notetaker determined dental fluorosis using the Thylstrup and Fejerskov criteria</p>	<p>Statistical analysis: NR</p> <p>Results: N (%) dental fluorosis absent</p> <ul style="list-style-type: none"> • <u>≤0.7 ppm F:</u> 306 (63.1) • <u>>0.7 ppm F:</u> 69 (55.2) <p>N (%) dental fluorosis present</p> <ul style="list-style-type: none"> • <u>≤0.7 ppm F:</u> 179 (36.9%) • <u>>0.7 ppm F:</u> 56 (44.8%) 	<p>“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)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sampling time frame:</p> <p>NR</p> <p>Sample size:</p> <p>610</p> <p>Sex N (%):</p> <p>Men: 329 (53.9%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Use fixed orthodontic appliance • Have reading difficulties • Have tooth malformations <p>Source of funding / support:</p>				

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

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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	N/A	Not applicable

Risk of bias assessment			
	study groups?		
	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 Thylstrup and 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

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	

Godebo 2020 [\[40\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross-sectional Country: Ethiopia Participants: Adolescents and adult	Exposures <u>Fluoride levels in</u> <ul style="list-style-type: none"> • Drinking water • Urine Exposure assessment: 24-hour urinary F- content was determined using the ion selective electrode	Outcome: Skeletal fluorosis Method of outcome ascertainment: <ul style="list-style-type: none"> • Bone scan in multiple skeletal sites, using a novel mobile non-ionizing ultrasound device. Results were examined using the 	Statistical analysis: <ul style="list-style-type: none"> • Bivariate and multivariable linear regression analyses • adjusted for age, sex, BMI, smoking, current tooth paste use Results: <ul style="list-style-type: none"> • 1 mg/L increase in F- in drinking water was related to reduction of 15.8 m/s (95% CI: 	<ul style="list-style-type: none"> • Negative associations between F- exposure and bone quality at all three bone sites • Fluoride-induced deterioration of bone quality in humans, likely reflecting a combination of factors related to SOS: net bone loss, abnormal mineralization and collagen formation, or altered

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>farmers living in the MER rural area</p> <p>Sampling time frame: 2018-2019</p> <p>Study population: 341</p> <p>Sex: (men): 55.1%</p> <p>Exclusions: individuals who were judged as incapable of undergoing detailed health examinations.</p> <p>Source of funding/support: National Institute of Environmental Health</p>	<p>and the hexamethyldisiloxane (HMDS)-facilitated diffusion method (Rango et al. 2017).</p> <p><u>Water F-</u> <u>concentrations: Mean (SD)</u></p> <ul style="list-style-type: none"> • <i>Water intake (liter/day): 1.3 ± 0.63</i> • <i>FI in groundwater (mg/L): 6.8 ±4.30</i> • <i>FI intake (mg/day): 9.13 ± 7.30</i> <p><u>Urinary F-</u> <u>concentrations: Mean (SD)</u> <i>F- in 24-h urine</i></p>	<p>same assessment criteria</p> <ul style="list-style-type: none"> • X-ray validation for a subset of participation, where radiographs were analyzed by a radiologist/co-author with a specialization in skeletal fluorosis 	<p>-21.3 to -10.3) of adult tibial SOS.</p> <ul style="list-style-type: none"> • 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 <p>Age, gender, and BMI were more significant predictors than in adults</p>	<p>microarchitecture.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sciences	(mg/L): 8.2 ± 7.6			
Author declaration of interest:	<i>F- excretion (mg):</i>			
Not reported	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	++	Yes (age, sex, BMI, smoking, current toothpaste use)

Risk of bias assessment			
	important confounding and modifying variables?		
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 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

Risk of bias assessment			
			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
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 [\[41\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u>	Outcome(s): Osteosarcoma (bone	Statistical analysis: • Conditional logistic regression to assess the	“Findings from this study demonstrated that

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Case-control</p> <p>Country: USA</p> <p>Participants: Phase 1</p> <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Water <p>Method of exposure assessment:</p> <p>NR</p> <p>Exposure level: Lived in a fluoridated area (0.7 ppm)</p> <ul style="list-style-type: none"> • No <ul style="list-style-type: none"> ○ Cases: 58 (24.6%) ○ Controls: 81 (19.8%) ○ <i>Reference</i> • Yes <ul style="list-style-type: none"> ○ Cases: 178 (75.4%) ○ Controls: 328 (80.2%) <p><i>OR: 0.76, 95% CI: (0.52 to 1.11), p-value: 0.156</i></p>	<p>cancer)</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Phase 1: histological confirmation of diagnosis followed by phone interviews • Phase 2: pathology reports 	<p>association of community water fluoridation with osteosarcoma.</p> <p>Results:</p> <ul style="list-style-type: none"> • A modestly significant interaction existed between fluoridation living status and bottled water use (P = 0.047). • Risk of osteosarcoma (adjusted): <ul style="list-style-type: none"> ○ 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 	<p>community water fluoridation is not associated with an increased risk for osteosarcoma.”</p>

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>department as cases.</p> <ul style="list-style-type: none"> • Controls were matched to cases on sex, age ± 5 years, and distance from the hospital <p>Sampling time frame:</p> <ul style="list-style-type: none"> • Phase 1: 1989–1993 • Phase 2: 1994–2000 <p>Sample size:</p> <ul style="list-style-type: none"> • Phase 1: cases (209), controls (440) • Phase 2: cases (108), controls (296) <p>Sex (N):</p> <p>Phase 1 & 2 combined:</p> <ul style="list-style-type: none"> • Cases: men: 142 (60.2%) 			<p>(95% CI: 0.54 - 6.41; P = 0.326).</p>	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none">• Controls: men 248 (60.6%) <p>Exclusions:</p> <p>Phase 1</p> <ul style="list-style-type: none">• Patients older than 40 years of age at diagnosis• Prior radiotherapy• Renal dialysis <p>Phase 2</p> <ul style="list-style-type: none">• Radiotherapy• Renal dialysis• Foreign nationals who were in the United States solely for treatment <p>Source of funding / support:</p> <ul style="list-style-type: none">• Statistical analysis: CDI				

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Research, Inc.</p> <ul style="list-style-type: none">• Phase 1: the National Institute of Environmental Health Sciences (NIH).• Data collection: the New England Research Institute.• Phase 2 was funded by the National Cancer Institute (NIH) and the National Institute of Dental and Craniofacial Research (NIH). <p>Author declaration of interest:</p> <p>Declaration of interest provided</p>				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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?	++ 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	N/A Not applicable

Risk of bias assessment			
	study?		
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Case-control study</p> <p>Country: India</p> <p>Participants: Patients (45 – 75 years of age) from RL Jalappa Hospital and Research Center</p> <p>Sampling time frame: July 2019 – September</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Serum <p>Method of exposure assessment: ISE Thermo Scientific Orion-5 Instrument</p> <p>Exposure level: Mean (SD) levels of fluoride in ppm by study groups</p> <p><u>Controls</u></p> <ul style="list-style-type: none"> • 0.0949 (0.12) <p><u>T2DM without CKD</u></p> <ul style="list-style-type: none"> • 0.6318 (0.59) 	<p>Outcome(s): Diabetes Mellitus and Diabetic nephropathy using serum renal parameters</p> <p>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”.</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Analysis conducted using one way Analysis of Variance test • Statistical significance at $p < 0.05$ <p>Results: Pearson correlation between serum fluoride and parameters (N = 30).</p> <p><u>Fasting Blood Sugar</u></p> <ul style="list-style-type: none"> • 0.28 <p><u>Postprandial Blood Sugar</u></p> <ul style="list-style-type: none"> • 0.44* <p><u>Urea</u></p> <ul style="list-style-type: none"> • 0.107 	<ul style="list-style-type: none"> • “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
2019	<u>T2DM with CKD</u>		<u>Serum Creatinine</u>	
	• 0.5128 (0.30)		• 0.08	
Sample size:	<u>p-value</u>		<u>Albumin</u>	
90	0.001		• 0.102	
			<u>Sodium</u>	
Sex:			• 0.005	
NR			<u>Potassium</u>	
			• 0.101	
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				
• Going through dialysis				
• Has acute kidney injury				
• Has hepatobiliary				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>disorder that result in proteinuria or albuminuria</p> <ul style="list-style-type: none"> • Has gestational DM, type 1 DM, or monogenic diabetic syndrome <p>Source of funding / support:</p> <p>NR</p> <p>Author declaration of interest:</p> <p>NR</p>				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
Selection	Was administered dose or exposure level	N/A Not applicable

Risk of bias assessment		
	adequately randomized?	
	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, hepatobiliary disorder resulting in proteinuria or albuminuria, gestational DM, DM type I, or

Risk of bias assessment			
			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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Ecological study</p> <p>Country: South Korea</p> <p>Participants: All residents in the Cheongju region</p> <p>Sampling time frame: 1 January 2004 - 31 December 2013</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Water <p>Method of exposure assessment: Data from the Korean Microdata Integrated Service (MIDS) of Statistics Korea.</p> <p>Exposure level: NR</p>	<p>Outcome(s):</p> <ul style="list-style-type: none"> • Hip fracture • Osteoporosis • Bone cancer <p>Method of outcome ascertainment: Data from the National Health Insurance Service (NHIS) for select ICD-10 codes.</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 <p>Results:</p> <ul style="list-style-type: none"> • The posterior relative risks (RR): <ul style="list-style-type: none"> ○ <u>Hip fracture:</u> RR: 0.95, 95% CI: 0.87- 1.05 	<p>“These findings suggest that CWF is not associated with adverse health risks related to bone diseases.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size:</p> <ul style="list-style-type: none"> • Fluoridated areas: 4,406,021 • Non-fluoridated areas: 2,270,959 <p>Sex (N):</p> <ul style="list-style-type: none"> • Fluoridated areas: Men: 2,200,104 (49.9%) • Non-fluoridated areas: Men: 1,126,495 (49.6%) <p>Exclusions:</p> <p>Reported no exclusions due to use of customized data from the NHIS</p>			<ul style="list-style-type: none"> ○ <u>Os\geqteoporosis</u> 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) <p>The RR of the selected bone diseases increased over time but did not increase in the CWF area compared to non-CWF areas.</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding / support:</p> <p>Division of Oral Health Policy, Ministry of Health and Welfare, Republic of Korea</p> <p>Author declaration of interest:</p> <p>No COI</p>				

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

Risk of bias assessment			
	concealed?		
	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
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

Risk of bias assessment			
			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 [\[44\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Serum	Outcome(s): CKDu	Statistical analysis: • Analysis conducted using the analysis of variance (ANOVA) test	• “CKDu patients showed significantly higher serum fluoride

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional</p> <p>Country: Sri Lanka</p> <p>Participants: Men with chronic kidney disease of uncertain aetiology (CKDu) and healthy controls</p> <p>Sampling time frame: NR</p> <p>Sample size (N): • Men with CKDu = 311 • Healthy Controls = 276</p>	<ul style="list-style-type: none"> • Water <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Drinking water samples from Girandurukotte and Medawachchiya • Blood samples from males with CKDu and healthy controls • Samples analyzed using fluoride ion-selective electrode <p>Exposure level: <i>Mean (SD) levels of fluoride in drinking water</i></p> <ul style="list-style-type: none"> • 0.68 mg/L (0.48) 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 or renal impairment, blood pressure not more than 140/90 mmHg, no proteinuria or glycosuria based on the dipstick 	<ul style="list-style-type: none"> • Statistical significance at $p \leq 0.05$ <p>Results: Mean serum fluoride level (SD) by CKDu stage</p> <p><u>Stage 0 (N = 276)</u></p> <ul style="list-style-type: none"> • 35.5 µg/L (16.3) <p><u>Stage 1 (N = 10)</u></p> <ul style="list-style-type: none"> • 38.1 µg/L (18.1) <p><u>Stage 2 (N = 60)</u></p> <ul style="list-style-type: none"> • 53.9 µg/L (34.2)* <p><u>Stage 3 (N = 160)</u></p> <ul style="list-style-type: none"> • 82.8 µg/L (41.9)* <p><u>Stage 4 (N = 72)</u></p> <ul style="list-style-type: none"> • 123.4 µg/L (59.9)* <p><u>Stage 5 (N = 9)</u></p>	<p>concentrations than the healthy controls.”</p> <ul style="list-style-type: none"> • “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
Sex: NR	<i>Mean (SD) levels of fluoride in serum by stages of CKD</i> <u>Stage 0 (N = 276)</u>	urine test, HbA1C<6.5%, serum creatinine <1.2 mg/dL and/ or A1M < 15.5 mg/L")	• 123.9 µg/L (52.6)* * p<0.05 compared to controls	
Exclusions: NR	• 35.5 µg/L (16.3) <u>Stage 1 (N = 10)</u>			
Source of funding / support: Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology	• 38.1 (18.1) <u>Stage 2 (N = 60)</u> • 53.9 (34.2)			
Author declaration of interest:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
No COI				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	N/A Not applicable

Risk of bias assessment			
	study?		
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 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cohort study</p> <p>Country: Scotland</p> <p>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</p>	<p>Exposures: Aluminum and fluoride levels in drinking water</p> <p>Method of exposure assessment: Data from the Drinking Water Quality Regulator for Scotland (DWQR)</p> <p>Fluoride in drinking water: <ul style="list-style-type: none"> • Mean: 53.4 µg/L ±16.0 • Range: 23.8–181.1 </p>	<p>Outcome: Dementia</p> <p>Method of outcome ascertainment: Any mention of <u>ICD-9 codes</u> 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 <u>ICD-10 codes:</u> F00-F05.1, F09, G30, and G3113 recorded on electronic medical records or death certificates after 2004, or from primary care records, specifically the</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Cox proportional hazards models for the association between aluminium and fluoride levels in drinking water 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. 	<ul style="list-style-type: none"> • “Higher levels of aluminium and fluoride were related to dementia risk in a population of men and women who consumed relatively low drinking-water levels of both.” • No statistical interaction between aluminium and fluoride levels in relation to dementia.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
(Scottish Mental Survey 1932) Sampling time frame: 2005-2014 Sample size (N): Initial: 37,597 Analysis: 6,980 Sex: N (%) Men: Initial: 19,272 (51%) Analysis: 2,728 (39%) Exclusions:		Greater Glasgow & Clyde Nursing Homes Medical Practice, which exclusively treated residents of nursing homes	<ul style="list-style-type: none"> • Additional model for the interaction between aluminium and fluoride. Results: <u>Out of an analytic sample of 2728 men and 4262 women alive in 2005:</u> <ul style="list-style-type: none"> • 622 men and 1350 women developed dementia. • All participants were approximately 84 years old at start of the exposure period • Follow-up duration: <ul style="list-style-type: none"> ○ <i>Mean: 2.7 years</i> 	<ul style="list-style-type: none"> • 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 highest quartile compared with the lowest.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants missing residential location, died before the monitoring period began in 2005, or missing childhood IQ test results</p> <p>Source of funding/ support:</p> <p>Alzheimer Scotland through the Marjorie MacBeath bequest</p> <p>Author declaration of interest: None</p>			<ul style="list-style-type: none"> ○ <i>SD: 2.1 years</i> ○ <i>Range: 0–7 years</i> • Fluoride <ul style="list-style-type: none"> ○ Mean: 53.4 µg/L ○ <i>SD: 16.0</i> ○ <i>Range: 23.8–181.1</i> 	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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

Risk of bias assessment			
			<p>confound the findings.</p> <p>No information could be identified regarding participants' exposure to drinking water before 2005, i.e., for the first 84 years of their lives.</p>
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?	++	<p>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</p>
Detection	Can we be confident in the exposure characterization?	++	<p>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).</p> <p>Sampling sites were identified by longitude and latitude and were widely distributed across</p>

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 [46]

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: cross-sectional (part of the Lithuanian National Oral Health Survey)</p> <p>Country: Lithuania</p> <p>Participants: Adults between 35 and 74 years old</p> <p>Sampling time frame: NR</p>	<p>Exposures: Fluoride levels in drinking water</p> <p>Method of exposure assessment: Fluoride levels in drinking water were provided by the water suppliers.</p> <p>Exposure level:</p> <ul style="list-style-type: none"> • ≤ 1 ppm • > 1 ppm 	<p>Outcome(s): Dental fluorosis</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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] 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 <p>Results:</p> <p>Dental fluorosis prevalence by age group and gender</p> <p><u>35–44 years</u></p> <p><i>Males</i></p> <ul style="list-style-type: none"> • Yes: 5 (4%) • No: 125 (96%) 	<p>“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).”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 1,397</p> <p>Sex: Men 462 (33.1%)</p> <p>Exclusions: NR</p> <p>Source of funding / support:</p> <p>The Borrow Foundation</p> <p>Author declaration of interest: No COI</p>			<p><i>Females</i></p> <ul style="list-style-type: none"> • Yes: 8 (4%) • No: 215 (96%) <p><u>45–54 years</u></p> <p><i>Males</i></p> <ul style="list-style-type: none"> • Yes: 2 (2%) • No: 102 (98%) <p><i>Females</i></p> <ul style="list-style-type: none"> • Yes: 3 (1%) • No: 204 (99%) <p><u>55–64 years</u></p> <p><i>Males</i></p> <ul style="list-style-type: none"> • Yes: 1 (1%) • No: 111 (99%) <p><i>Females</i></p> <ul style="list-style-type: none"> • Yes: 0 (0%) • No: 248 (100%) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<u>65-74 years</u> <i>Males</i> <ul style="list-style-type: none"> • Yes: 2 (2%) • No: 114 (98%) <i>Females</i> <ul style="list-style-type: none"> • Yes: 0 (0%) • No: 253 (100%) Dental fluorosis prevalence by water fluoride level ≤ 1 ppm	
			<u>35-44 years</u> <ul style="list-style-type: none"> • Males: 121 (93%) • Females: 198 (88%) <u>45-54 years</u> <ul style="list-style-type: none"> • Males: 95 (91%) • Females: 181 (87%) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<u>55–64 years</u> <ul style="list-style-type: none"> • Males: 100 (89%) • Females: 201 (80%) 	
			<u>65-74 years</u> <ul style="list-style-type: none"> • Males: 96 (83%) • Females: 204 (80%) 	
			>1ppm	
			<u>35–44 years</u> <ul style="list-style-type: none"> • Males: 9 (7%) • Females: 26 (12%) 	
			<u>45–54 years</u> <ul style="list-style-type: none"> • Males: 9 (9%) • Females: 26 (13%) 	
			<u>55–64 years</u> <ul style="list-style-type: none"> • Males: 12 (11%) • Females: 49 (20%) 	
			<u>65-74 years</u> <ul style="list-style-type: none"> • Males: 20 (17%) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			• Females: 50 (20%)	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	N/A Not applicable

Risk of bias assessment			
	study?		
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 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: China</p> <p>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 with fluoride levels < 1.0 mg/L)</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Urine <p>Method of exposure assessment: Fluoride ion-selective electrode</p> <p>Exposure level: NR</p>	<p>Outcome(s):</p> <ul style="list-style-type: none"> • Reduction of bone mineral density (BMD) via CALCA gene methylation <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • BMD: Standalone ultrasound bone densitometer • CALCA methylation: Quantitative methylation-specific polymerases chain reaction 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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) <p>Results:</p> <p>Adjusted association of fluoride with CALCA exon 1 methylation levels</p> <ul style="list-style-type: none"> • $r = 0.022$ 	<p>“...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.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
in Tongxu County			• p = 0.576	
Sampling time frame:			Adjusted association (β ;	
NR			95% CI) of fluoride (mg/L)	
			with CALCA exon 1	
			methylation levels by age	
Sample size:			groups	
722			<u>20 – 60 yrs</u> (N = 722)	
			• 0.270 (-0.621, 1.162)	
Sex (%):			<u>20 – 39 yrs</u> (N = 135)	
Women: 100%			• 1.656 (-1.464, 4.776)	
			<u>40 – 44 yrs</u> (N = 70)	
Exclusions:			• 4.953 (1.162, 8.743)	
• Had “history of chronic			<u>45 – 49 yrs</u> (N = 139)	
bone disease, bone			• -0.152 (-2.673, 2.369)	
fracture, cognitive			<u>50 – 54 yrs</u> (N = 220)	
impairment, chronic			• 0.405 (-0.797, 1.607)	
kidney disease”			<u>55 – 60 yrs</u> (N = 158)	
• Were using				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>bisphosphonates</p> <ul style="list-style-type: none"> • Had incomplete data <p>Source of funding / support:</p> <ul style="list-style-type: none"> • National Natural Science Foundation of China • Scientific and Technological Project of Henan Province <p>Author declaration of interest:</p> <p>No COI</p>			<ul style="list-style-type: none"> • -1.643 (-3.657, 0.370) <p>Correlation between fluoride and T-score</p> <ul style="list-style-type: none"> • $r = 0.019$ • $p = 0.611$ <p>Adjusted association (β; 95% CI) of fluoride (mg/L) with T-score by age groups</p> <p><u>20 – 60 yrs</u> (N = 722)</p> <ul style="list-style-type: none"> • 0.010 (-0.032, 0.051) <p><u>20 – 39 yrs</u> (N = 135)</p> <ul style="list-style-type: none"> • 0.001 (-0.139, 0.139) <p><u>40 – 44 yrs</u> (N = 70)</p> <ul style="list-style-type: none"> • 0.106 (-0.021, 0.233) <p><u>45 – 49 yrs</u> (N = 139)</p> <ul style="list-style-type: none"> • 0.095 (-0.022, 0.212) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>50 – 54 yrs</u> (N = 220)</p> <ul style="list-style-type: none"> • -0.063 (-0.129, -0.002) <p><u>55 – 60 yrs</u> (N = 158)</p> <ul style="list-style-type: none"> • 0.035 (-0.044, 0.114) <p>Interaction between fluoride and CALCA exon 1 methylation on BMD was assessed</p> <ul style="list-style-type: none"> • “...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 ($\beta = 5.338$, $P = 0.016$)” 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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
	Were the research personnel and human subjects blinded to the study group during the	N/A Not applicable

Risk of bias assessment			
	study?		
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 appropriate and researchers adhered to the study protocol)?	++	None identified

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cohort study</p> <p>Country: Canada</p> <p>Participants: English-/French-speaking women, >17 years old, and less than 14 weeks gestation were recruited from prenatal clinics in 10 Canadian cities (Maternal-Infant Research on Environmental</p>	<p>Exposures: Fluoride levels in</p> <ul style="list-style-type: none"> • Drinking water • Urine samples (maternal) <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Water fluoride concentrations recorded in municipal water reports. • Maternal urinary fluoride (MUF) adjusted for specific gravity as a proxy of fetal fluoride exposure. <p>Water Fluoride</p>	<p>Outcomes: Intellectual function</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 IQ, and Performance IQ (PIQ) 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 <p>Results:</p>	<p>“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.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
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) Sex: Children: girls <i>Breastfed, fl: 51%</i> <i>Breastfed, non-fl: 53%</i> <i>Formula, fl: 54%</i>	concentration (mg/L) <u><i>Breastfed</i></u> ≥ 6 <i>mo.</i> • Fluoridated: 0.58 (0.08) • Non- Fluoridated: 0.13 (0.06) <u><i>Formula-fed</i></u> • Fluoridated: 0.59 (0.07) • Non- Fluoridated: 0.13 (0.05) P-value: 0.18 Infant fluoride intake (mg/day) <u><i>Breastfed</i></u> ≥ 6 <i>mo.</i> • Fluoridated: 0.12 (0.07)		• Thirty-eight percent of mother-child dyads lived in fluoridated communities. • An increase of 0.5 mg/L in water fluoride concentration (<i>almost equal to the difference between fluoridated and non-fluoridated regions</i>) corresponded to reduction in performance IQ: ○ <u><i>Formula-fed:</i></u> 9.3-point (95% CI: -13.77, -4.76) ○ <u><i>Breastfed:</i></u> 6.2-point (95% CI:	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p><i>Formula, non-fl: 47%</i></p> <p>Exclusions:</p> <p>Participants with known fetal abnormality, had any medical complications, or known illicit drug use during pregnancy.</p> <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • National Institute of Environmental Health Science (NIEHS) • Health Canada • Ontario Ministry of the Environment, • CIHR 	<p>• Non- Fluoridated: 0.02 (0.02)</p> <p><i>Formula-fed</i></p> <p>• Non- Fluoridated: 0.34 (0.12)</p> <p>• Non- Fluoridated: 0.08 (0.04)</p> <p>P-value: <.001</p>		<p>-10.45, -1.94).</p> <p>• Association remained significant upon controlling for fetal fluoride exposure</p> <ul style="list-style-type: none"> ○ <i>Formula-fed:</i> (B=-7.93, 95% CI: -12.84, -3.01) ○ <i>Breastfed:</i> (B=-6.30, 95% CI: -10.92, -1.68) 	

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

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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.
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

Risk of bias assessment			
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?	++	<p>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)</p> <p>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)</p>
Detection	Can we be confident in the exposure characterization?	+	<p>Yes, data on levels of fluoride exposure were consistently drawn within the same timeframe, from the same source: municipal water reports.</p> <p>Maternal urinary fluoride (MUF) adjusted for specific gravity (non-validated) was used as a</p>

Risk of bias assessment			
			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

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 fluorosis areas in Tianjin, China. Sampling time frame: 2015	Exposures: Fluoride levels in <ul style="list-style-type: none"> • Drinking water • Urine samples Method of exposure assessment: <ul style="list-style-type: none"> • 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 analyzer EA940 with a 	Outcomes: <ul style="list-style-type: none"> • Thyroid hormone dysfunction (TT3, TT4, FT3, FT4 and TSH levels in serum) • Intelligence (IQ) Method of outcome ascertainment: <ul style="list-style-type: none"> • Chemiluminescent microparticle immunoassay on the ARCHITECT i4000SR was employed to quantify thyroid hormone levels in serum. 	Statistical analysis: <ul style="list-style-type: none"> • 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:	“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
<p>Sample size (N): 571</p> <p>Sex: Boys: 292 (51.1%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • 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, Treponema palladium, Down's syndrome) 	<p>fluoride ion selective electrode (Wu et al., 2015).</p> <p>Water fluoride level: Mean (mg/L): 1.39 ±1.01</p>	<ul style="list-style-type: none"> • A Combined Raven's Test for Rural China (CRT-RC2) was taken to evaluate the IQ of each child 	<p>(Mean ± SD)</p> <p><u>Fluoride</u></p> <ul style="list-style-type: none"> • Water fluoride (mg/L) <ul style="list-style-type: none"> ○ 1.39 ± 1.01 • Urinary fluoride (mg/L) <ul style="list-style-type: none"> ○ 1.28 ± 1.30 <p><u>Thyroid hormones:</u></p> <ul style="list-style-type: none"> • TT3 (ng/mL): <ul style="list-style-type: none"> ○ 1.32 ± 0.19 • FT3 (pg/mL): <ul style="list-style-type: none"> ○ 3.28 ± 0.32 • TT4 (µg/dL): <ul style="list-style-type: none"> ○ 6.86 ± 1.16 • FT4 (ng/dL): <ul style="list-style-type: none"> ○ 1.13 ± 0.12 • TSH (uIU/mL): <ul style="list-style-type: none"> ○ 2.57 ± 1.29 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Exposure to smoking and drinking during maternal pregnancy <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • State Key Program of National Natural Science of China • National Natural Science Foundation of China • Fundamental Research Funds for the Central Universities <p>Author declaration of interest:</p> <p>No COI</p>			<ul style="list-style-type: none"> • Every 1 mg/L increment of water fluoride was associated with <ul style="list-style-type: none"> ○ 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 • Every 1 mg/L increment of urinary fluoride was associated with <ul style="list-style-type: none"> ○ 0.007 ng/mL increase in TT3 ○ 0.02 pg/mL 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><i>increase in FT3</i></p> <ul style="list-style-type: none"> ○ <i>0.09 ng/mL</i> <p><i>decrease in TT4</i></p> <ul style="list-style-type: none"> ○ <i>0.009 ng/mL</i> <p><i>decrease in FT4</i></p> <ul style="list-style-type: none"> ○ <i>0.11 μIU/mL</i> <p><i>increase in TSH</i></p> <ul style="list-style-type: none"> ● Fluoride exposure was inversely related to IQ scores <ul style="list-style-type: none"> ○ <i>Water fluoride:</i> <i>B=-1.59 (95% CI: -2.61, -0.57)</i> ○ <i>Urinary fluoride:</i> <i>B=-1.21 (95% CI: -1.99, -0.44).</i> ● Higher TT3, FT3 were related to the increased 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>odds of children having high normal intelligence</p> <ul style="list-style-type: none"> ○ <i>TT3</i> <i>OR=3.41 (95% CI: 1.04, 11.12)</i> ○ <i>FT3</i> <i>OR=3.277 (95% CI: 1.62, 6.62)</i> <p>• A significant modification effect by TSH on the association between urinary fluoride and IQ scores, without mediation by thyroid hormones</p>	

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		
Attrition	Were outcome data complete without	++	There was no loss of participants due to attrition	

Risk of bias assessment

	attrition or exclusion from analysis?		
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
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
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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross-sectional Country: China (Henan Pr)	Exposures: <u>Fluoride levels in</u> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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. 	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
<p>Participants:</p> <ul style="list-style-type: none"> • 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). 	<p>a fluoride ion-selective electrode (Shanghai Exactitude, Shanghai, China) assay was used to measure urine fluoride levels.</p>	<p>(R&D systems, Minneapolis, USA) was used to measure serum concentrations of SHBG and ABP.</p>	<ul style="list-style-type: none"> • The genotypic distribution of ESRα among control subjects accorded with the Hardy-Weinberg equilibrium (P=0.193, P_{vull}; P=0.050, X_{bal}; P=0.410, rs3798577). • Analysis adjusted for age, diet, exercise habits, tobacco use, alcohol and tea consumption <p>Results:</p> <p><u>Water fluoride (Mean \pm SD)</u></p> <ul style="list-style-type: none"> • Group of villages with high exposure (HEG): 	<p>ABP levels vary depending on ESRα gene polymorphisms</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sampling time frame:</p> <p>2011-2012</p> <p>Sample size (N):</p> <p>348</p> <p>Sex:</p> <p>Males (100%)</p> <p>Exclusions:</p> <p>Participants who resided in other places for at least 1 year, had a history of chronic bone disease, underwent bisphosphonate, hormonal or calcitonin</p>			<p><i>2.44±1.88 mg/L</i></p> <p>• Group of villages with low exposure (LEG):</p> <p><i>0.37± 0.15 mg/L</i></p> <p><u>Urinary fluoride (Mean ± SD)</u></p> <p>• Fluoride (mg/L)</p> <ul style="list-style-type: none"> ○ <i>HEG 2.66 ± 1.03</i> ○ <i>LEG 0.95 ± 0.31</i> <p><i>P-value: <0.001</i></p> <p><u>Reproductive hormones (Mean ± SD)</u></p> <p>• ABP (nmol/L)</p>	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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?	++	<ul style="list-style-type: none"> • 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?	+	<ul style="list-style-type: none"> • Analyses were adjusted for age, urinary fluoride level, diet, exercise habits, tobacco use, alcohol and tea consumption

Risk of bias assessment			
			<ul style="list-style-type: none"> • 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)
Selective	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of

Risk of bias assessment			
reporting			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

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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Fluoride levels in drinking water	Outcomes: Secondary bone cancer	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 contiguity for generating	We found no evidence of an association between community water fluoridation category and secondary bone cancer from 2008
Study design: Ecological study	Method of exposure assessment: Data from the water quality reports from	Method of outcome ascertainment: Data on inpatient cancer patients admitted with an ICD9		
Country:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>USA (NY State)</p> <p>Participants:</p> <p>+18 years old inpatients with metastatic bone cancer who were admitted to a New York State hospital for receiving care</p> <p>Sampling time frame:</p> <p>January 1, 2008 – December 31, 2010</p> <p>Sample size (N):</p> <p>24,661</p>	<p>individual providers in the different NY State counties</p>	<p>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)</p>	<p>spatial weights.</p> <ul style="list-style-type: none"> Series of regression models with county-level percentage of secondary bone cancer as the dependent variable <p>Results:</p> <p><u>Fluoride in drinking water:</u></p> <ul style="list-style-type: none"> 0.7 mg/L (45 counties) 0.8 mg/L (2 counties) 0.5 mg/L (1 county) 0.4 mg/L (1 county) <p><u>Percentage of population in county with fluoridation</u></p> <ul style="list-style-type: none"> <25% 	<p>to 2010 at the county level in New York State</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> ○ <i>No. counties: 27</i> ○ <i>2^{ry} bone cancer: 12.9%</i> ○ <i>Coefficient: ref</i> ○ <i>p-value: -</i> 	
Sex:				
Exclusions:				
Patients with incomplete zip code, patient identification code, patient's New York State residency status or less than 18 years old			<ul style="list-style-type: none"> ● <i>25%-75%</i> ○ <i>No. counties: 16</i> ○ <i>2^{ry} bone cancer: 12.9%</i> ○ <i>Coefficient: 0.02</i> ○ <i>p-value: 0.96</i> 	
Source of funding/ support:				
Not reported			<ul style="list-style-type: none"> ● <i>>75%</i> ○ <i>No. counties: 19</i> ○ <i>2^{ry} bone cancer: 12.9</i> 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Author declaration of interest: Not reported			% ○ Coefficient: 0.02 ○ p-value: 0.97	

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
Confounding	Did the study design or analysis account for important confounding and modifying variables?	++	No accounting for confounders or appropriate standardization reported

Risk of bias assessment			
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?	++	<ul style="list-style-type: none"> • 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.
	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

Risk of bias assessment			
			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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Case-control</p> <p>Country: Sri Lanka</p> <p>Participants: Cases: 19-76 years old, non-dialysis, biopsy-proven definite CKDu cases, recruited from Girandurukotte and Wilgamuwa renal</p>	<p>Exposures: Fluoride level in serum</p> <p>Method of exposure assessment: ion-selective electrode (94-09 BNWP) with Orion Star A329 Ionalyzer (Thermo Orion MA, USA) after dilution with an equal volume of commercially available TISAB III buffer (Thermo Orion 940911).</p>	<p>Outcomes: Chronic kidney disease of unknown origin (CKDu), using fluoride level in urine</p> <p>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 removed by centrifugation.</p>	<p>Statistical analysis: • Descriptive statistics</p> <p>Results: • Water fluoride ○ Fluoride in ground water: 1.33 - 5.30 mg/L ○ Fluoride MAC in drinking water: 0.60 mg/L</p> <p>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>	<p>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.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
clinics. Controls (matched): Healthy volunteers			<ul style="list-style-type: none"> ○ $p = 0.000$ (showed a significant difference based on CKDu stage but not with sex or age) 	
Sampling time frame: Nor reported				
Sample size (N): 193 (116 cases and 77 controls)			<p>Urinary fluoride: Mean \pmSD [range] mg/L</p> <ul style="list-style-type: none"> ○ CKDu patients: 1.53 ± 0.8 [0.45 – 6.92] ○ Controls: 1.26 ± 0.63 [0.36 – 3.80] ○ $p = 0.004$ 	
Sex: Cases: Men (81.1%) Controls: Men (70.1%)				<ul style="list-style-type: none"> ● Patients in the age group 19–29 years showed lower serum fluoride levels than other
Exclusions:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Not reported			age groups	
<p>Source of funding/ support:</p> <p>National Research Council (NRC) Target Orient research Grant</p> <p>Author declaration of interest:</p> <p>No COI</p>				

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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?	+	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
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	+	Yes, the outcome was assessed in cases and controls

Risk of bias assessment			
	assessment?		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 [\[53\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Fluoride levels in • Drinking water	Outcomes: • Vascular alterations using the carotid	Statistical analysis: • Multiple linear regression	• Fluoride exposure is related to early vascular alterations, which

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional</p> <p>Country: Mexico (Chihuahua)</p> <p>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: 0.18 mg/L) or Aldama (fl: 2 mg/L), where there is no concurrent exposure to arsenic</p>	<ul style="list-style-type: none"> • Urine samples <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<p>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)</p> <ul style="list-style-type: none"> • 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)] <p>Method of outcome</p>	<ul style="list-style-type: none"> • Adjusted for urinary specific gravity, BMI, age and sex <p>Results:</p> <ul style="list-style-type: none"> • Water fluoride: Mean (IQR): <ul style="list-style-type: none"> ○ 0.3 mg/mL (0.01–1.9) Maximum permissible limit: <ul style="list-style-type: none"> ○ 1.5 <p>Urinary fluoride showed</p> <ul style="list-style-type: none"> • Positive association with <ul style="list-style-type: none"> ○ eGFR ($\beta=1.3$, $p=0.015$), ○ VCAM-1 ($\beta=111.1$, 	<p>may increase the susceptibility of cardiovascular diseases in adult life.</p> <ul style="list-style-type: none"> • Inconclusive results regarding fluoride exposure and kidney injury

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sampling time frame: November 2015</p> <p>Sample size (N): 374</p> <p>Sex: Boys: 46.8%</p> <p>Exclusions: Children with a previous diagnosis of chronic diseases</p> <p>Source of funding/support:</p>	<p>reference material (U-F-0907 and U-F1510), Centre de Toxicologie du Quebec) and controls were used for quality control.</p> <p><u>Blood analysis</u></p> <ul style="list-style-type: none"> Biochemical analysis (glucose, lipid profile, uric acid and creatine) was performed by an automatic analyser (Prestige 24i, Tokyo Boeki Medical System Ltd., Tokyo, Japan). <p><u>Urine analysis</u></p>	<p>ascertainment:</p> <ul style="list-style-type: none"> 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). 	<p>$p=0.019$</p> <ul style="list-style-type: none"> ICAM-1 ($\beta=57$, $p=0.032$) cIMT ($\beta=0.01$, $p=0.032$) <p>• Inverse association with</p> <ul style="list-style-type: none"> uCys-C ($\beta=-8.5$, $p=0.043$) sCys-C ($\beta=-9.6$, $p=0.021$) <p>• No significant association with</p> <ul style="list-style-type: none"> ET-1 ($\beta=0.069$, $p=0.074$) KIM-1 ($\beta=29.1$, $p=0.212$) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> Children's Environmental Health Network National Council of Science and Technology, Mexico <p>Author declaration of interest: No COI</p>	<ul style="list-style-type: none"> First morning void urine was used Specific gravity was measured immediately using a refractometer (PAL-10S, ATAGO®, Tokyo, Japan) Urine analysis was performed with a urine analyser (U-66, Mindray Co., Shenzhen, China). 			

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

Risk of bias assessment			
	concealed?		
	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
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.

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

Jimenez-Cordova 2019a [\[54\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Fluoride levels in drinking water	Outcomes: Urinary concentrations of inorganic arsenic	Statistical analysis: <ul style="list-style-type: none"> Multiple linear regression Adjusted for urinary specific gravity, age, sex, BMI and smoking 	Fluoride exposure decreases Arsenic methylation capacity, and increases its toxicity
Study design: Cross-sectional	Method of exposure assessment:	Method of outcome ascertainment:		

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: Mexico</p> <p>Participants: Adult participants residing in Chihuahua for 1 or more years, were directly recruited from information sessions</p> <p>Sampling time frame: 2013</p> <p>Sample size (N): 236</p>	<p>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).</p>	<p>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 (Hernández-Zavala et al., 2008).</p>	<p>Results:</p> <p>Water fluoride: <i>1.6 mg/L ±1.6</i></p> <p>Urinary fluoride: <i>2.8 µg/L±2.8</i></p> <p>A statistically significant interaction of F and As exposure on the following was observed:</p> <ul style="list-style-type: none"> • Increase in MAs% ($\beta = 0.16, p = 0.018$) • Decrease in DMAs% ($\beta = -0.3, p = 0.034$), • Decrease in PMI ($\beta=-0.07, p=0.052$) • Decrease in SMI 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			($\beta=-0.13$, $p=0.097$)	
<p>Sex: Men: 29%</p> <p>Exclusions: Non-residents of Chihuahua province</p> <p>Source of funding/ support: National Council of Science and Technology, Mexico</p> <p>Author declaration of interest: No COI</p>				

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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
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

Risk of bias assessment			
	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 appropriate and researchers adhered to the study protocol)?	++	None identified

Khanoranga 2019 [\[55\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Ground water samples • Urinary samples	Outcome(s): Dental fluorosis Method of outcome	Statistical analysis: • Relationship between fluoride level and DF was conducted using Pearson's	"The relationship among the groundwater fluoride concentration, urinary F, and dental

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Cross-sectional study</p> <p>Country: Pakistan</p> <p>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</p> <p>Sampling time frame: August – September 2017</p>	<p>Method of exposure assessment: Ion selective electrode method</p> <p>Exposure level: Fluoride levels (mg/L) found in groundwater samples of the three districts (Quetta Pishin, and Mastung)</p> <ul style="list-style-type: none"> • Range: 0.87 – 1.59 <p>Mean (SD) Fluoride levels (mg/L) found in urinary samples of participants from the three districts and controls</p>	<p>ascertainment:</p> <ul style="list-style-type: none"> • Single dentist conducted DF examination using the WHO Dean’s Index • CFI was calculated as: \sum (Number of people x Dean numerical weight) / Total number of people examined 	<p>correlation</p> <p>Results:</p> <ul style="list-style-type: none"> • Correlation between groundwater fluoride levels and CFI $r = 0.90$ • Correlation between urinary fluoride levels and CFI $r = 0.96$ 	<p>fluorosis was assessed through Pearson’s correlations. A strong positive relationship was determined by the aforementioned parameters (groundwater F, urinary F, and dental fluorosis)” (p. 419)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sample size:	<u>Quetta (n = 25)</u>			
<u>Brick kiln workers</u>	<ul style="list-style-type: none"> • Mean: 0.17 (0.15) • Range: 0.013 – 0.54 			
100				
<u>Controls</u>	<u>Pishin (n = 50)</u>			
20	<ul style="list-style-type: none"> • Mean: 0.19 (0.21) • Range: 0.002 – 0.842 			
Sex:	<u>Mastung (n = 25)</u>			
Men: 100%	<ul style="list-style-type: none"> • Mean: 0.30 (0.19) • Range: 0.092 – 0.811 			
Exclusions: NR	<u>Control (n = 20)</u>			
	<ul style="list-style-type: none"> • Mean: 0.003 (0.002) • Range: 0.0003 – 0.007 			
Source of funding / support: NR				
Author declaration of interest: NR				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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 [\[56\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Fluoride levels in ground	Outcomes: age- and sex-	Statistical analysis: • Multivariable linear and	• low-to-moderate fluoride exposure

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional</p> <p>Country: China</p> <p>Participants: Randomly selected 7–13 years old residents from low to-moderate fluorosis, ground water-supplied areas of Baodi District, Tianjin, China</p> <p>Sampling time frame: May - October 2015</p>	<p>water and urine</p> <p>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)</p>	<p>standardized height, weight and BMI z-scores, and childhood overweight/obesity (BMI z-score > 1)</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 	<p>logistic regression analyses</p> <ul style="list-style-type: none"> • 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 	<p>is associated with overweight and obesity in children.</p> <ul style="list-style-type: none"> • Gender and paternal education level may modify the relationship

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size (N): 2,430</p> <p>Sex: Boys: 51.1%</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • History of chronic medical illness (e.g. renal, hepatic, and endocrine disorders), • Long-term medication related to overweight and obesity were not included 		<p>measured using a standard dual reading scale.</p> <ul style="list-style-type: none"> • 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>post-term birth</p> <p>Results:</p> <ul style="list-style-type: none"> • Water fluoride: <ul style="list-style-type: none"> ○ 0.83 mg/L (95%CI: 0.81, 0.86) ○ p-value: 0.414 • Urinary fluoride <ul style="list-style-type: none"> ○ 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 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding/ support:</p> <ul style="list-style-type: none"> • National Natural Science of China • National Natural Science Foundation of China • Fundamental Research Funds for the Central Universities <p>Author declaration of interest:</p> <p>No COI</p>			<p>(Ptrend=0.022).</p> <ul style="list-style-type: none"> • Each log unit (roughly 10-fold) increase in urinary fluoride concentration was associated with a <ul style="list-style-type: none"> ○ <i>0.136 unit increase in weight z-score (95% CI: 0.039, 0.233)</i> ○ <i>0.186 unit increase in BMI z-score (95% CI: 0.058, 0.314)</i> ○ <i>1.304-fold increased odds of overweight/obesity (95% CI: 1.062, 1.602)</i> ○ <i>These associations were stronger in girls than in boys (P</i> 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><i>interaction= 0.016)</i></p> <ul style="list-style-type: none"> ○ <i>Children of fathers with lower education levels were more vulnerable to fluoride (P interaction=0.056)</i> <ul style="list-style-type: none"> ● 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			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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
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

Risk of bias assessment			
	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 [\[57\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Fluoride in drinking water and serum	Outcomes: • Estimated glomerular filtration rate • Serum uric acid	Statistical analysis: • Multiple linear regression • Adjusted for age, sex,	Fluoride exposure may contribute to complex changes in kidney and liver related parameters
Study design:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Cross-sectional</p> <p>Country: United States</p> <p>Participants: US adolescents: 12–19 years old (NHANES survey)</p> <p>Sampling time frame: 2013–2016</p> <p>Sample size (N): 4,470</p>	<p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Albumin to creatinine ratio • Blood urea nitrogen • AST/ALT • ALP • Gamma-glutamyl transferase • Serum albumin <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 	<p>race, BMI, family income, daily protein intake and serum cotinine (biomarker of tobacco smoke exposure)</p> <p>Results:</p> <ul style="list-style-type: none"> • Tap water fluoride $0.48 \text{ mg/L} \pm 0.03$ • Plasma fluoride $0.40 \text{ } \mu\text{mol/L} \pm 0.01$ • A 1 mg/L increase in water fluoride was associated with: <ul style="list-style-type: none"> ○ 0.93 mg/dL lower blood urea nitrogen concentration (95% CI: $-1.44, -0.42$; 	<p>among US adolescents</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sex:</p> <p>Men: 52.7%</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Institutionalized persons • Suggestive kidney diseases • Not drinking tap water • insufficient or excessive protein intake <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • Mount Sinai Children's Center Foundation • NIH/NIEHS 		<p>Synchron chemistry analyzer was utilized; while from 2015 to 2016 a Beckman Coulter UniCel DxC 660i Synchron Access chemistry analyzer was utilized as well.</p> <ul style="list-style-type: none"> • 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. 	<p><i>p=0.007).</i></p> <ul style="list-style-type: none"> ○ <i>eGFR: -1.03 mL/min/m² (95% CI: -2.93, 0.87); p > 0.99;</i> <i>water fluoride was log₂ transformed in this model.</i> ○ <i>SUA: 0.05 mg/dL (95% CI: -0.07, 0.18); p > 0.99</i> ○ <i>ACR: -0.01 mg/g (95% CI: -0.07, 0.06); p = > 0.99; water fluoride and outcome variables were log₂ transformed.</i> • 1 μmol/L increase in plasma fluoride was associated with: <ul style="list-style-type: none"> ○ 10.36 mL/min/1.73m² 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Author declaration of interest: No COI			<p><i>lower estimated glomerular filtration rate (95% CI: -17.50, -3.22; p=0.05)</i></p> <ul style="list-style-type: none"> <i>0.29 mg/dL higher serum uric acid concentration (95% CI: 0.09, 0.50; p=0.05)</i> <i>1.29 mg/dL lower blood urea nitrogen concentration (95%CI: -1.87, -0.70; p < 0.001)</i> 	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 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	+

Risk of bias assessment				
			and urine. Lack of blinding of outcome assessors would not appreciably bias results.	correlation (human 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 [\[58\]](#)

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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional</p> <p>Country: US</p> <p>Participants: 16-19 years old adolescents with fluoride biomonitoring data and self-reported sleep outcome measures (NHANES 2015–2016)</p> <p>Sampling time frame:</p>	<p>water and serum</p> <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<p>outcome measures</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 	<p>and multinomial logistic regression analyses</p> <ul style="list-style-type: none"> • Adjusted for age, sex, body mass index (BMI), race/ethnicity, and the ratio of family income to poverty <p>Results:</p> <ul style="list-style-type: none"> • Tap water fluoride mean (SE): <i>0.39 mg/L (0.05)</i> • Plasma fluoride mean (SE): <i>0.35 μmol/L (0.02)</i> <p>Median (IQR) for:</p> <ul style="list-style-type: none"> • Water fluoride: 	<p>cycle regulation and sleep behaviors among older adolescents in the US.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
2015–2016	electrometrically with an ion-specific electrode		0.27 (0.52) mg/L	
Sample size (N): 419			• Plasma fluoride 0.29 (0.19) $\mu\text{mol/L}$	
Sex: Men: 49.08			• An IQR increase in water fluoride was associated with	
Exclusions:			○ 1.97 times higher odds of reporting symptoms suggestive of sleep apnea (95% CI: 1.27, 3.05; $p = 0.02$)	
• Not consuming tap water			○ 24 min later bedtime ($B = 0.40$, 95% CI: 0.10, 0.70; $p = 0.05$)	
• Consuming sleep medications			○ 26 min later morning wake time ($B = 0.43$, 95% CI: 0.13, 0.73; $p = 0.04$)	
• No fluoride samples				
Source of funding/support:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
NIH/NIEHS			○ Among males, a 38% reduction in the odds of reporting snoring (95% CI: 0.45, 0.87, p =0.03).	
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: China</p> <p>Participants: Residents aged 16 or older who lived in one of five villages that are endemic in skeletal fluorosis, (Zhao Dong</p>	<p>Exposures:</p> <ul style="list-style-type: none"> • Fluoride levels in drinking water • Skeletal fluorosis <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<p>Outcomes: Genetic biomarkers of skeletal fluorosis</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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, 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Descriptive statistics <p>Results:</p> <ul style="list-style-type: none"> • Water fluoride groups: <ul style="list-style-type: none"> ○ 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- 	<ul style="list-style-type: none"> • 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
County, Heilongjiang Province) Sampling time frame: NR Sample size (N): 302 Sex: Men: 30% Exclusions: <ul style="list-style-type: none"> • Bone diseases • Hypertension • Atherosclerosis • Heart disease 	(GB 5750.5-2006, China). <ul style="list-style-type: none"> • Urinary fluoride was also assessed by using 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 	CA, USA) was performed according to the manufacturer's instructions. <ul style="list-style-type: none"> • Quantitative PCR was performed using a TaqMan miRNA PCR kit (Haigene, Harbin, China) on an ABI7500 Fast Realtime PCR system (ABI, USA). 	regulated and 10 miRNAs were down-regulated <ul style="list-style-type: none"> • 3 additional miRNAs (miR-200c-3p, miR-1231 and miR-3185) were significantly up-regulated in the cases 	molecular pathways is still not very clear

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Diabetes <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • 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 	investigation			

Study Characteristics

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

Risk of bias assessment

<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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	

Risk of bias assessment			
Attrition	Were outcome data complete without attrition or exclusion from analysis?	++	There was no attrition or 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, 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design Cross-sectional study</p> <p>Country Canada</p> <p>Participants Persons Youth 6-17 years old from the Canadian Health Measures Survey (Cycles 2 and 3).</p> <p>Study name • Canadian Health Measures Survey (CHMS)</p>	<p>Exposures <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Community source • Tap water • Urine <p>Method of exposure ascertainment <u>Community water fluoridation status (CWF)</u></p> <p>Acquired from city website reports or water treatment plant</p> <p><u>Urinary fluoride (UF_{SG}):</u> non-fasting spot samples</p> <p><u>Tap water fluoride</u> Samples from participants' home during Cycle 3</p>	<p>Outcome Attention-related outcomes</p> <p>Method of outcome ascertainment</p> <ul style="list-style-type: none"> • 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 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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
<p>Sampling timeframe</p> <ul style="list-style-type: none"> • 2009–2011 • 2012–2013 <p>Sample size (N)</p> <ul style="list-style-type: none"> • Cycle 2: N=2,520 • Cycle 3: N=2,667 <p>Sex (%)</p> <p>Men: 50.8%–52.7%</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Resided in home for ≤ 2 years • Reside in place with mixed city fluoridation status Consume bottled water • Consume well rather 	<p>Mean (SD) concentration of urinary fluoride adjusted for specific gravity (mg/L)</p> <ul style="list-style-type: none"> • <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) <p>Mean (SD) concentration of water fluoride (mg/L)</p> <ul style="list-style-type: none"> • <u>Urinary fluoride – sample 1</u> 0.23 (0.24) • <u>CWF status – sample 2</u> 0.26 (0.26) 	<p>participants 6 to 11 years of age</p> <ul style="list-style-type: none"> • Among those 12 to 17 years of age, outcome information was acquired from the participants themselves 	<p>exposure at home, and log₁₀-transformed lead level in blood)</p> <p>Results</p> <ul style="list-style-type: none"> • Water fluoride <i>Mean ±SD: 0.23 mg/L ±0.24 (cycles 3 only)</i> • Urinary fluoride <i>Mean ±SD: 0.61 mg/L ±0.39 (cycles 2 & 3)</i> <ul style="list-style-type: none"> • 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 	


Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>than municipal water</p> <ul style="list-style-type: none"> Remove fluoride with home filtration system <p>Source of funding: Faculty of Health, York University</p> <p>Conflict of interest: No COI</p>	<ul style="list-style-type: none"> Tap water fluoride – <u>sample 3</u> 0.23 (0.24) <p>Mean (SD)</p> <ul style="list-style-type: none"> Urinary fluoride 11.3 (3.4) CWF status 11.3 (3.3) Tap water fluoride 11.2 (3.5) 		<p>predict ADHD</p> <p>$aOR=0.96$ (95% CI: 0.63, 1.46); $p=0.84$</p> <ul style="list-style-type: none"> UF_{SG} did not significantly predict SDQ hyperactive/inattentive subscale scores <p>$aOR = 0.31$ (-0.04, 0.66); $p = 0.08$</p> <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> UF_{SG} did not significantly 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>predict ADHD</p> <p>$aOR=0.96$ (95% CI: 0.63, 1.46); $p=0.84$</p> <ul style="list-style-type: none"> • UF_{SG} did not significantly predict SDQ hyperactive/inattentive subscale scores <p>$aOR = 0.31$ (-0.04, 0.66); $p = 0.08$</p> <p><u>ADHD diagnosis & tap water fluoride</u></p> <ul style="list-style-type: none"> • $aOR = 6.10$ (1.60, 22.8); $p < 0.05$ • Exposure-response relationship: yes <p><u>SDQ hyperactive/inattentive subscale score & tap water</u></p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>fluoride</u></p> <ul style="list-style-type: none"> • aOR = 0.31 (0.04, 0.58); p < 0.05 • Exposure-response relationship: yes <p><u>ADHD diagnosis & UF_{SG}</u></p> <ul style="list-style-type: none"> • aOR = 0.96 (0.63, 1.46); p < 0.05 • Exposure-response relationship: yes <p><u>SDQ</u></p> <p><u>Hyperactive/Inattentive</u></p> <p><u>Subscale Score & UF_{SG}</u></p> <ul style="list-style-type: none"> • aOR = 0.31 (-0.04, 0.66); p = 0.05 Exposure-response relationship: yes 	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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	++	Not considered a risk of bias as it documented the

Risk of bias assessment			
	attrition or exclusion from analysis?		exclusion of those who reported drinking bottled water as 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 were appropriate and researchers adhered	++	None identified

Risk of bias assessment	
	to the study protocol)? 

Shaik 2019 [\[61\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross-sectional Country: India Participants:	Exposures: Fluoride levels in drinking water Method of exposure assessment: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Serum T3, T4 was determined with Competitive Chemi Luminescent Immunoassay kits 	Statistical analysis: <ul style="list-style-type: none"> Descriptive analyses Results: <ul style="list-style-type: none"> Water fluoride mean: <i>Group I (0.01-0.6 ppm):</i> 0.22 <i>Group II (0.7-1.2 ppm):</i> 0.89 <i>Group III (1.3-2.0 ppm):</i> 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
<p>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</p> <p>Sampling time frame: NR</p> <p>Sample size (N): 293</p> <p>Sex: Boys: 46%</p>		<ul style="list-style-type: none"> • Serum TSH was determined with Ultra-Sensitive Sandwich Chemi-Luminescent Immunoassay with analyzer according to the manufacturer recommendation. 	<ul style="list-style-type: none"> • 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
<p>Exclusions:</p> <p>Non-resident children, and those with substandard growth or health status</p> <p>Source of funding/ support:</p> <p>NR</p> <p>Author declaration of interest:</p> <p>No COI</p>				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>

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?	+	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 or 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.
Selective reporting	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of

Risk of bias assessment			
			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 [\[62\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Drinking water samples • Urine samples	Outcome(s): • Intellectual ability • Dental fluorosis	Statistical analysis: • Statistical significance at $p < 0.05$	• “No evidence was found for fluoride-associated cognitive deficits. As the level of fluoride consumption remains a public health concern and its implications for health are still
Study design: Cross-sectional study	Method of exposure assessment: • Ion selective electrode	Method of outcome ascertainment: • Intellectual ability: Raven’s Colored Progressive Matrices	Results: • Mean (\pm SD) water fluoride levels (mg/L) by dental fluorosis categories ○ $TF\ 0: 0.75 \pm 0.95$	
Country: Mexico				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Participants: Children (9 to 10 years of age) in grade 4 attending public elementary schools in Chihuahua</p> <p>Sampling time frame: May – December 2017</p> <p>Sample size: 161</p> <p>Sex: Men: 88 (54.7%)</p> <p>Exclusions: • Received topical fluoride</p>	<p>Exposure level: See results for exposure levels by dental fluorosis and intellectual ability categories</p>	<p>(RCPM)</p> <p>Dental fluorosis: Thylstrup-Fejerskov (TF) Index used to examine vestibular, occlusal, and lingual surfaces</p>	<ul style="list-style-type: none"> ○ <i>TF 1 – 2: 0.67 ± 0.15</i> ○ <i>TF 3 – 4: 1.22 ± 1.09</i> ○ <i>TF > 5: 1.66±0.93</i> ○ <i>p-value: 0.008</i> <ul style="list-style-type: none"> • Mean (\pmSD) urinary fluoride levels (mg/L) by dental fluorosis categories <ul style="list-style-type: none"> ○ <i>TF 0: 0.48 ± 0.23</i> ○ <i>TF 1 – 2: 0.51 ± 0.38</i> ○ <i>TF 3 – 4: 0.62 ± 0.32</i> ○ <i>TF > 5: 0.67±0.41</i> ○ <i>p-value: 0.088</i> • Mean (\pmSD) exposure dose to fluoride (EDI) (mg/kg bw/day) by dental fluorosis categories <ul style="list-style-type: none"> ○ <i>TF 0: 0.016 ± 0.02</i> ○ <i>TF 1 – 2: 0.017 ± 0.02</i> ○ <i>TF 3 – 4: 0.035 ± 0.03</i> 	<p>uncertain, further research is needed to clarify whether or not fluoride may possibly have adverse effects on brain development.” (p. 481)</p> <ul style="list-style-type: none"> • “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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>application in last 6 months</p> <ul style="list-style-type: none"> • Have different residence since time of pregnancy • Have mental illness diagnosis • Have systemic disorder diagnosis <p>Source of funding / support:</p> <p>PRODEP program of the Mexican Minister of Education (SEP)</p> <p>Author declaration of interest:</p> <p>No COI</p>			<ul style="list-style-type: none"> ○ $TF > 5: 0.047 \pm 0.03$ ○ $p\text{-value}: 0.001$ <ul style="list-style-type: none"> • Mean (\pmSD) water fluoride levels (mg/L) by IQ categories <ul style="list-style-type: none"> ○ $Grade I: 1.48 \pm 1.13$ ○ $Grade II: 1.05 \pm 1.06$ ○ $Grade III: 1.04 \pm 1.06$ ○ $Grade IV: 0.97 \pm 1.10$ ○ $Grade V: 0.79 \pm 1.17$ ○ $p\text{-value}: 0.645$ • Mean (\pmSD) urinary fluoride levels (mg/L) by IQ grade categories <ul style="list-style-type: none"> ○ $Grade I: 0.45 \pm 0.34$ ○ $Grade II: 0.54 \pm 0.29$ ○ $Grade III: 0.61 \pm 0.38$ ○ $Grade IV: 0.56 \pm 0.33$ ○ $Grade V: 0.35 \pm 0.19$ 	<p>statistically significant difference was present.” (p. 477 – 478)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> ○ <i>p</i>-value: 0.559 ● Mean (\pmSD) exposure dose/daily intake by IQ grade categories <ul style="list-style-type: none"> ○ <i>Grade I</i>: 0.03 \pm0.03 ○ <i>Grade II</i>: 0.026 \pm0.03 ○ <i>Grade III</i>: 0.027 \pm0.03 ○ <i>Grade IV</i>: 0.029 \pm0.03 ○ <i>Grade V</i>: 0.016 \pm0.02 ○ <i>p</i>-value: 0.389 	

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

Risk of bias assessment				
	concealed?			
	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	++	Yes,	outcome ++ Yes, outcome (dental

Risk of bias assessment			
	assessment?		(IQ/intellectual ability) 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.
			fluorosis) was measured by a single examiner, assisted by a recorder, using the Thysstrup 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional</p> <p>Country: US</p> <p>Participants: Massachusetts (MA) resident women with a live birth (2009- 2016) who responded to the PRAMS survey (Pregnancy Risk</p>	<p>Exposures:</p> <ul style="list-style-type: none"> •Dental cleaning during pregnancy (DC) alone •Community water fluoridation (CWF) alone •DC and CWF combined <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> •DC: PRAMS survey questionnaire •CWF: MA Dept. of Public Health, Office of Oral Health 	<p>Outcomes:</p> <p>Prevalence of preterm births (birth < 37 weeks gestation)</p> <p>Method of outcome ascertainment:</p> <p>Derived from the infant’s birth certificate</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> •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) <p>Results:</p> <ul style="list-style-type: none"> •Water fluoride levels: NR 	<p>Women who had dental cleaning during pregnancy and lived in a community with water fluoridation had lower prevalence of preterm birth.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Assessment Monitoring System)</p> <p>Sampling time frame: 2009-2016</p> <p>Sample size (N): 9,234</p> <p>Sex: Women: 100%</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Women with multiple births • Missing data for dental 			<ul style="list-style-type: none"> • Prevalence of preterm birth among women with a singleton live birth was 8.5% in Massachusetts. • 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: <ul style="list-style-type: none"> ○ <i>Dental cleaning alone and preterm birth: significant (aRR = 0.74 [95% CI 0.55–0.98])</i> ○ <i>CWF alone and preterm birth: non-</i> 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>cleaning during pregnancy, CWF, and/or gestational age</p> <ul style="list-style-type: none"> • Missing data on relevant maternal characteristics <p>Source of funding/ support:</p> <p>CDC</p> <p>Author declaration of interest:</p> <p>NR</p>			<p><i>significant (aRR = 0.81 [95% CI 0.63–1.05])</i></p> <ul style="list-style-type: none"> ○ <i>DC–CWF and preterm birth: significant (aRR = 0.74 [95% CI 0.57–0.95]) were significant</i> 	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
Selection	Was administered dose or exposure level	N/A	

Risk of bias assessment			
	adequately randomized?		
	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.
Detection	Can we be confident in the exposure	++	Yes, exposure was consistently measured using the

Risk of bias assessment			
	characterization?		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 [\[64\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: Fluoride levels in drinking water	Outcomes: Prevalence of one of seven eye diseases	Statistical analysis: • Multiple logistic regression analysis	• High intake of fluoride may act directly and/or indirectly on the

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design:</p> <p>Cross-sectional</p> <p>Country:</p> <p>China</p> <p>Participants:</p> <p>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</p> <p>Sampling time frame:</p>	<p>Method of exposure assessment:</p> <p>Fluoride levels in the blood, urine, and drinking-water</p>	<p>Method of outcome ascertainment:</p> <p>Complete ocular examination</p>	<ul style="list-style-type: none"> Adjusted for age, smoking, drinking habits, blood pressure, BMI, education, and annual income. <p>Results:</p> <ul style="list-style-type: none"> Drinking-water fluoride: >1.2 mg/L Fluoride in the drinking water was closely associated with: <ul style="list-style-type: none"> Cataract: OR: 0.543 (95% CI 0.310–0.845). Pterygium: OR: 1.991 (95% CI 1.931–3.622). 	<p>eyeball.</p> <ul style="list-style-type: none"> 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
NR			<ul style="list-style-type: none"> ○ <i>Arteriosclerotic retinopathy: OR: 2.011 (95% CI 1.121–3.637).</i> ○ <i>Primary angle closure glaucoma: OR:1.179 (95% CI: 0.788–1.489).</i> ○ <i>Diabetic retinopathy: OR: 1.845 (95% CI: 0.931–3.120).</i> ○ <i>Age-related macular degeneration: OR: 1.048 (95% CI: 0.735–2.221).</i> ○ <i>Strabismus: OR: 1.598 (95% CI: 0.936–2.689).</i> 	
Sample size (N): 1,813				
Sex: Men: 30%				
Exclusions:				
<ul style="list-style-type: none"> • Less than 10 years of residence • congenital eye disease or ocular trauma 				
Source of funding/ support:				<ul style="list-style-type: none"> • Compared to the control

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> Center for Endemic Disease Control Chinese Center for Disease Control and Prevention <p>Author declaration of interest: No COI</p>			<p>group:</p> <ul style="list-style-type: none"> 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 exposed group, 6.4% in control group). Non-significant associations with primary angle closure glaucoma, diabetic 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			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 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	

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?	++	There was no attrition or 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
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: China</p> <p>Participants: Children (7 to 13 years to age), from rural areas with low-to-moderate fluoride exposure in Tianjin</p> <p>Sampling time frame:</p>	<p>Exposures:</p> <p><u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Drinking water samples • Urine samples <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • National standardized ion selective electrode method <p>Exposure level in mg/L (P25 – P75):</p> <p><u>Non-DF group</u></p> <ul style="list-style-type: none"> • Water: 0.70 (0.40 – 0.80) • Urine: 0.17 (0.09 – 0.31) 	<p>Outcome(s):</p> <ul style="list-style-type: none"> • Genotoxicity (Mitochondrial DNA (mtDNA) levels) • Dental fluorosis (DF) <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • <u>mtDNA</u>: quantitative real-time polymerase chain reaction assay • <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 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 • Association of DF with water and urinary fluoride levels were adjusted for age, gender, BMI, LBW, maternal education, paternal education, and family income 	<p>“In conclusion, we have showed that low-to-moderate concentrations of water fluoride and urinary fluoride were positively associated with DF prevalence, while inversely 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,</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
2015	<u>DF group</u>			and that the reduced mtDNA levels may partly mediate the elevated prevalence of moderate DF in children under such exposure.”
Sample size:	<ul style="list-style-type: none"> • Water: 1.60 (1.20 – 2.60) • Urine: 2.11 (0.45 – 2.69) 		Results:	
616			mtDNA	
Sex N (%):			• Change (95% CI) in mtDNA levels among those with water fluoride levels in T2 and T3 compared to T1 (mg/L)	
<u>Non-DF group</u>			<u>T1 (≤ 0.70)</u>	
Men: 109 (45.4%)			Reference	
			<u>T2 (0.71 – 1.50)</u>	
<u>DF group</u>			B = -0.24 (-0.32, -0.15)	
Men: 202 (53.7%)			P = 0.035	
Exclusions (from analysis):			<u>T3 (> 1.50)</u>	
• Have cavities			B = -0.32 (-0.39, -0.24)	
• Have orthodontic appliances			P <0.001	
			<u>Trend test</u>	
			P <0.001	
			• Change (95% CI) in mtDNA levels per 1 mg/L increase in water fluoride	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Source of funding / support:</p> <ul style="list-style-type: none"> • The State Key Program of National Natural Science of China • The National Natural Science Foundation of China <p>The Fundamental Research Funds for the Central Universities</p> <p>Author declaration of interest:</p> <p>NR</p>			<p>level</p> <p>B = -0.10 (-0.14, -0.06)</p> <p>P <0.001</p> <ul style="list-style-type: none"> • Change (95% CI) in mtDNA levels among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <p><u>T1 (≤ 0.21)</u></p> <p>Reference</p> <p><u>T2 (0.22 – 2.08)</u></p> <p>B = -0.03 (-0.12, 0.06)</p> <p>P = 0.516</p> <p><u>T3 (> 2.08)</u></p> <p>B = -0.27 (-0.35, -0.20)</p> <p>P <0.001</p> <p><u>Trend Test</u></p> <p>P <0.001</p> <ul style="list-style-type: none"> • Change (95% CI) in mtDNA levels per 1 mg/L increase in urinary fluoride level 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>B = -0.12 (-0.14, -0.09)</p> <p>P <0.001</p> <p>Total DF</p> <ul style="list-style-type: none"> • Odds (95% CI) of total DF among those with water fluoride levels in T2 and T3 compared to T1 (mg/L) <p><u>T1 (≤ 0.70)</u> Reference</p> <p><u>T2 (0.71 – 1.50)</u> OR = 2.58 (2.02, 3.30) P <0.001</p> <p><u>T3 (> 1.50)</u> OR = 3.64 (2.91, 4.55) P <0.001</p> <p><u>Trend Test</u> P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of total DF per 1 mg/L increase in 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>water fluoride level</p> <p>OR = 1.47 (1.40, 1.55)</p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of total DF among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <p><u>T1 (≤ 0.21)</u></p> <p>Reference</p> <p><u>T2 (0.22 – 2.08)</u></p> <p>OR = 1.49 (1.26, 1.77)</p> <p>P <0.001</p> <p><u>T3 (> 2.08)</u></p> <p>OR = 3.16 (2.53, 3.95)</p> <p>P <0.001</p> <p><u>Trend Test</u></p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of total DF per 1 mg/L increase in urinary fluoride level 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			OR = 1.39 (1.32, 1.46) P <0.001 Very Mild DF <ul style="list-style-type: none"> 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> OR = 4.93 (3.48, 6.98) P <0.001 <u>Trend Test</u> P <0.001 <ul style="list-style-type: none"> Odds (95% CI) of very mild DF per 1 mg/L increase in 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>water fluoride level</p> <p>OR = 1.85 (1.63, 2.11)</p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of very mild DF among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <p><u>T1 (≤ 0.21)</u></p> <p>Reference</p> <p><u>T2 (0.22 – 2.08)</u></p> <p>OR = 1.31 (0.92, 1.86)</p> <p>P = 0.135</p> <p><u>T3 (> 2.08)</u></p> <p>OR = 4.02 (2.81, 5.74)</p> <p>P <0.001</p> <p><u>Trend Test</u></p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of very mild DF per 1 mg/L increase in urinary fluoride level 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>OR = 1.57 (1.41, 1.76)</p> <p>P <0.001</p> <p><i>Mild DF</i></p> <ul style="list-style-type: none"> • Odds (95% CI) of mild DF among those with water fluoride levels in T2 and T3 compared to T1 (mg/L) <p><u>T1 (≤ 0.70)</u></p> <p>Reference</p> <p><u>T2 (0.71 – 1.50)</u></p> <p>OR = 4.17 (2.80, 6.20)</p> <p>P <0.001</p> <p><u>T3 (> 1.50)</u></p> <p>OR = 6.88 (4.78, 9.92)</p> <p>P <0.001</p> <p><u>Trend Test</u></p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of mild DF per 1 mg/L increase in 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>water fluoride level</p> <p>OR = 1.68 (1.57, 1.79)</p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of mild DF among those with urinary fluoride levels in T2 and T3 compared to T1 (mg/L) <p><u>T1 (≤ 0.21)</u></p> <p>Reference</p> <p><u>T2 (0.22 – 2.08)</u></p> <p>OR = 1.79 (1.44, 2.23)</p> <p>P <0.001</p> <p><u>T3 (> 2.08)</u></p> <p>OR = 5.99 (4.15, 8.66)</p> <p>P <0.001</p> <p><u>Trend Test</u></p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of mild DF per 1 mg/L increase in urinary fluoride level 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>OR = 1.56 (1.45, 1.67)</p> <p>P <0.001</p> <p>Moderate DF</p> <ul style="list-style-type: none"> • Odds (95% CI) of moderate DF per 1 mg/L increase in water fluoride level <p>OR = 3.85 (3.01, 4.92)</p> <p>P <0.001</p> <ul style="list-style-type: none"> • Odds (95% CI) of moderate DF per 1 mg/L increase in urinary fluoride level <p>OR = 2.85 (2.39, 3.39)</p> <p>P <0.001</p>	

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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, 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 investigation period)

Risk of bias assessment			
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?	++	<p>* Yes, outcome (dental fluorosis) was measured independently by two dentists using Dean's Fluorosis Index.</p> <p>* 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).</p> <p>* Lack of blinding of outcome assessors would not appreciably bias results.</p>
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Prospective cohort study</p> <p>Country: Mexico</p> <p>Participants: Mother-child pairs residing in Mexico City enrolled in two of four cohorts of the Early Life Exposures to Environmental</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Maternal urinary samples (prenatal fluoride exposure biomarker) <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • ≥ 1 second morning void spot urine sample from gestational period was used and adjusted for creatinine • Number of participants (N) with 	<p>Outcomes:</p> <ul style="list-style-type: none"> • Attention-deficit/hyperactivity disorder (ADHD) related symptoms in children between 6 to 12 years of age <p>Method of outcome ascertainment:</p> <p><u>Conners' Rating Scales-Revised (CRS-R)</u></p> <ul style="list-style-type: none"> • Completed by mothers • Used to evaluate ADHD related 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Multivariate gamma regression models were used • 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) 	<p>Positive association between higher prenatal fluoride 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</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Toxicants (ELEMENT) study; specifically, participants from cohorts 2A and 3 were included in the analysis.</p> <p>Sampling time frame:</p> <p><u>Cohort 2A:</u></p> <ul style="list-style-type: none"> • 1997 to 1999 <p><u>Cohort 3:</u></p> <ul style="list-style-type: none"> • 2001 to 2003 <p>Sample size (N): 213 Mother-child pairs</p>	<p>maternal urinary fluoride measures adjusted for creatinine by trimester:</p> <p><u>1st Trimester:</u> N = 175</p> <p><u>2nd Trimester:</u> N = 80</p> <p><u>3rd Trimester:</u> N = 62</p> <ul style="list-style-type: none"> • Number of participants (N) by number of measurements <p><u>3 measurements:</u> N = 14</p> <p><u>2 measurements:</u></p>	<p>behaviours</p> <ul style="list-style-type: none"> • Scores the following: Cognitive Problems + Inattention, Restless-Impulsive, Hyperactivity, ADHD Index, DSM-IV Inattention, DSM-IV Hyperactivity-Impulsivity, and DSM-IV ADHD Total <p><u>Conners' Continuous Performance Test, 2nd edition (CPT-II)</u></p> <ul style="list-style-type: none"> • Completed by children • Used to evaluate sustained attention and inhibitor control • Scores the following: 	<p>Results:</p> <p>Change (95% CI) in outcome per 0.5 mg/L unit increase in maternal urinary fluoride levels adjusted for creatinine</p> <ul style="list-style-type: none"> • CRS-R scores (N = 210) <p><u>Cognitive Problems + Inattention</u> $\beta = 2.54 (0.44, 4.63)$ $p = 0.0178$</p> <p><u>Restless-Impulsive</u> $\beta = 1.92 (-0.07, 3.91)$ $p = 0.0586$</p> <p><u>Hyperactivity</u></p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sex: Girls: <ul style="list-style-type: none"> • N (%) = 116 (54) Exclusions: <ul style="list-style-type: none"> • 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 	N = 78 <u>1 measurement:</u> N = 122 Exposure levels: <ul style="list-style-type: none"> • Mean (95% CI) level of fluoride in maternal urine adjusted for creatinine 0.85 mg/L (0.81, 0.90) 	Omission Errors, Commission Errors, and Hit Reaction Time <u>Other Details</u> <ul style="list-style-type: none"> • 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 	$\beta = 1.05$ (-0.91, 3.00) $p = 0.2953$ <u>ADHD Index</u> $\beta = 2.47$ (0.43, 4.50) $p = 0.0175$ <u>DSM-IV Inattention</u> $\beta = 2.84$ (0.84, 4.84) $p = 0.0054$ <u>DSM-IV Hyperactivity-Impulsivity</u> $\beta = 1.69$ (-0.33, 3.70) $p = 0.1016$ <u>DSM-IV ADHD Total</u> $\beta = 2.38$ (0.42, 4.34) $p = 0.0176$ <ul style="list-style-type: none"> • CPT-II scores (N = 210) <u>Omission Errors</u> $\beta = 0.22$ (-2.30, 2.74)	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>by the mother</p> <p>Source of funding/ support:</p> <p>U.S. NIH, NIEHS/EPA, and the National Institute of Public Health/Ministry of Health of Mexico; facilities provided by the American British Cowdray Hospital</p> <p>Author declaration of interest: NR</p>			<p>$p= 0.8643$</p> <p><u>Commission Errors</u></p> <p>$\beta= -0.43 (-2.38,$ $1.51)$</p> <p>$p= 0.6641$</p> <p><u>Hit Reaction Time</u></p> <p>$\beta= 1.07 (-1.19, 3.32)$</p> <p>$p= 0.3546$</p>	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 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

Risk of bias assessment				
			sensitivity analysis.	
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?	++	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	++ Participants were recruited at 14 gestational weeks or

Risk of bias assessment

			<p>gestational weeks or less, and outcomes were measured in children between 6 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</p>		<p>less, and outcomes were measured in children between 6 to 12 years of age; regression models 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.</p>
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Risk of bias assessment			
			psychologist oversaw the psychometric tests. However, missing 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.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: China</p> <p>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</p>	<p>Exposure: Fluoride levels in urine samples</p> <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Morning urine samples were collected • Measured using ion selective electrode method <p>Exposure levels: Median (interquartile range) levels of fluoride</p>	<p>Outcomes: Intelligence quotient (IQ)</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • In the overall participants, the 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>drinking water) and non-endemic (0.20 – 1.00 mg/L levels of fluoride in drinking water) fluorosis.</p> <p>Sampling time frame: 2014 – 2015</p> <p>Sample size (N): 323</p> <p>Sex: <u>Boys:</u> • N (%) = 177 (54.8)</p> <p>Exclusions:</p>	<p>in urine by DRD2 single nucleotide polymorphism (SNP)</p> <ul style="list-style-type: none"> • <u>CC (N = 103)</u> 1.3 (0.9 – 1.6) • <u>CT (N = 179)</u> 1.2 (0.8 – 1.8) • <u>TT (N = 44)</u> 1.3 (1.0 – 2.0) 	<p>Borderline: 70 – 79 Low average: 80 – 89 Average: 90 – 109 High average: 110 – 119 Good: 120 – 129 Excellent: ≥ 30</p>	<p>of TT was adjusted for age of child and having a cold</p> <ul style="list-style-type: none"> • Robust estimates of variance were acquired using a bootstrap procedure <p>Result:</p> <ul style="list-style-type: none"> • Change (95% CI) in IQ score per log-unit increase in urinary fluoride among all participants and by subgroups <p><u>Overall (N = 323)</u> β = -2.47 (-4.93, -0.01) p = 0.049</p>	<p>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.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Informed consent forms not signed by guardians • Moved • No measurement of dopamine receptor-2 (DRD2) genotyping <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • National Nature Science Foundation of China • Scientific and Technological Project of Tianjin Medicine in 2014 • Scientific and Technological Project 			<p>[Bootstrapped estimate: 95%CI = -4.97, 0.03; p = 0.053]</p> <p><u>DRD2 SNP of CC or CT (N = 279)</u></p> <p>$\beta = -1.59$ (-4.24, 1.05) p = 0.236</p> <p>[Bootstrapped estimate: 95%CI = -4.14, 0.95; p = 0.220]</p> <p><u>DRD2 SNP of TT (N = 44)</u></p> <p>$\beta = -12.31$ (-18.69, -5.94) p = < 0.001</p> <p>[Bootstrapped</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
of Tianjin Centers for Disease Control and Prevention			estimate: 95%CI = -19.66, -4.96; p = 0.001]	
Author declaration of interest: None			<ul style="list-style-type: none"> “...the safety threshold of urine fluoride levels in the subgroup TT was 1.73 mg/L (95% CI = (1.51 mg/L, 1.97 mg/L))” (p. 276) 	

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

Risk of bias assessment			
	concealed?		
	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 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

Risk of bias assessment			
			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 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.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: Mexico</p> <p>Participants: Adult (18 to 77 years of age) residents of 3 Chihuahua communities (El Sauz, Aldama, and Gpe. Victoria) exposed to fluoride via drinking</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Drinking water samples • Urine samples <p>Co-exposure: <u>Arsenic levels in</u></p> <ul style="list-style-type: none"> • Urine samples <p>Method of exposure assessment: <u>Fluoride levels in water and urine samples</u></p> <ul style="list-style-type: none"> • Potentiometric method using ion 	<p>Outcomes: <u>Kidney injury</u></p> <ul style="list-style-type: none"> • Urine levels of albumin (ALB), cystatin-C (Cys-C), kidney injury molecule 1 (KIM-1), clusterin (CLU), osteopontin (OPN), and trefoil factor 3 (TIFF-3) <p><u>Kidney function</u></p> <ul style="list-style-type: none"> • Glomerular filtration rate (eGFR) <p>Method of outcome</p>	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Multiple linear regression analysis was used • Interaction analysis between fluoride and tAS was conducted • 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 	<ul style="list-style-type: none"> • "...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. 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
<p>water</p> <p>Sampling time frame: July 2013</p> <p>Sample size (N): 239</p> <p>Sex: <u>Men</u></p> <p>• N (%) = 68 (28.8)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • < 18 years of age • Infrequent consumption of tap water 	<p>selective electrode</p> <p><u>Inorganic arsenic and corresponding metabolite levels in urine samples</u></p> <ul style="list-style-type: none"> • Hydride generation-cryotrapping-atomic absorption spectrometry using Perkin Elmer Analyst 400 spectrometer and multi-atomizer • Total urinary arsenic (tAS) is the sum of inorganic arsenic and corresponding metabolites monomethylarsonic acid (MAs) or 	<p>ascertainment:</p> <p><u>eGFR</u></p> <ul style="list-style-type: none"> • 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 <p><u>Urinary kidney damage biomarkers</u></p> <ul style="list-style-type: none"> • First morning void samples used • Luminex xMAP Technology using MILLIPLEX MAP 	<ul style="list-style-type: none"> • 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 • KIM-1 models were 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Live in study area for < 1 year • Have cancer or kidney disease <p>Source of funding/support: Mexican National Council of Science and Technology</p> <p>Author declaration of interest: None</p>	<p>dimethylarsinic acid (DMAs)</p> <p><u>Normalization of fluoride and tAS levels in urine</u></p> <ul style="list-style-type: none"> • Levine-Fahy method and urinary strip specific gravity <p>Exposure levels:</p> <ul style="list-style-type: none"> • Geometric mean (Interquartile range; IQR) level of water fluoride (mg/L); N = 232 1.5 (0.19 – 1.8) • Geometric mean (IQR) level of urinary fluoride (µg/mL); N = 	<p>Human Kidney Toxicity panel 3 and 4</p> <ul style="list-style-type: none"> • Biomarker levels in urine were adjusted for specific gravity and Creatinine 	<p>adjusted for specific gravity, amorphous urate crystals, mucoprotein, atherogenic index, and age</p> <ul style="list-style-type: none"> • 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 <p>Results:</p> <ul style="list-style-type: none"> • Change in outcome 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
	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)		(p-value) per unit increase of fluoride in water (mg/L) and urine ($\mu\text{g/mL}$) <u>ALB ($\mu\text{g/mL}$)</u> Water: $\beta= 1.20$ ($p=$ <0.001) Urine: $\beta= 0.56$ ($p=$ <0.001) <u>Cys-C ($\mu\text{g/mL}$)</u> Water: $\beta= 0.03$ ($p=$ 0.005) Urine: $\beta= 0.022$ ($p=$ 0.001) <u>OPN ($\mu\text{g/mL}$)</u> Water: $\beta= 0.10$ ($p=$ 0.028) Urine: $\beta= 0.038$ ($p=$ 0.041)	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<u>CLU (µg/mL)</u> Water: $\beta = 0.09$ ($p = 0.118$) Urine: $\beta = 0.07$ ($p = 0.100$)	
			<u>KIM-1 (ng/mL)</u> Water: $\beta = 0.045$ ($p = 0.162$) Urine: $\beta = 0.048$ ($p = 0.008$)	
			<u>TFF-3 (ng/mL)</u> Water: $\beta = 2.88$ ($p = 0.010$) Urine: $\beta = 1.14$ ($p = 0.115$)	
			<u>eGFR (mL/min/1.73 m²)</u> Water: $\beta = 0.19$ ($p =$	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			0.675) Urine: $\beta = 0.49$ ($p = 0.030$)	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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

Risk of bias assessment			
			was assessed for potential interaction with 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?	++	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	Were all measured outcomes reported?	++	Yes, outcomes mentioned in the abstract were

Risk of bias assessment			
reporting			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.

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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross-sectional study	Exposures: <u>Fluoride levels in</u> <ul style="list-style-type: none"> • water • Serum • Urine Method of exposure	Outcomes: <u>Thyroid functional activity</u> <ul style="list-style-type: none"> • Serum levels of free triiodothyronine (T3), free thyroxine (T4), and thyroid stimulating hormone 	Statistical analysis: <ul style="list-style-type: none"> • Chi-square and Mann Whitney tests • Results considered significant at $p < 0.05$ Results:	<ul style="list-style-type: none"> • 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: India</p> <p>Participants: Children (8 to 15 years of age) from endemic fluorosis area and fluorosis non-endemic area</p> <p>Sampling time frame: NR</p> <p>Sample size (N): 400</p> <p>Group A (N = 200): Subjects from endemic fluorosis area</p> <p>• A1 (N = 100): Subjects with dental</p>	<p>assessment:</p> <ul style="list-style-type: none"> • Manual titration method, automatic analyzer, and radiometer <p>Exposure levels:</p> <ul style="list-style-type: none"> • 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 	<p>(TSH)</p> <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Immuno Chemiluminescence Mircroparticle Assay with Autoanalyzer 	<ul style="list-style-type: none"> • Mean free T3 (pg/ml) by study group A: 3.125; B: 2.698 p = 0.26 • Mean free T4 (ng/dL) by study group A: 1.282; B: 1.193 p = 0.41 • Mean TSH (μIU/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>of group 2 (p-value < 0.05).</p> <ul style="list-style-type: none"> • Fluorosis and thyroid functional activity are positively correlated with each other. • Excessive fluoride levels also lead to alteration in thyroid hormones activity

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
fluorosis • 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	• Range of serum fluoride (ppm) level by study groups A1: 0.05 – 0.71 A2: 0.05 – 0.71 B: 0.03 – 0.10		p = 0.02 • Mean serum fluoride (ppm) by study group A: 0.195; B: 0.059 p = 0.03 • Percent (%) of thyroid hormone level derangement by study group A: 67.5; B: 54	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>type of dental staining, and medication use that interferes with thyroid</p> <p>Source of funding/ support: None</p> <p>Author declaration of interest: None</p>				

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 children 8 to 15 years of age. Information on recruitment time frame and participation rate 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?	++	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	++	Thyroid hormones were measured in serum, and

Risk of bias assessment			
	assessment?		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.
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.

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Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Water samples	Outcome(s): Severity of Dental Fluorosis (DF)	Statistical analysis: • Logistic regression analysis conducted to examine association between DF and potential risk factors	“The severity of dental fluorosis is positively correlated with the fluoride content in the water. The water fluoride content is the
Study design: Cross-sectional study	Method of exposure assessment:	Method of outcome ascertainment:	• Model variables include	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: India</p> <p>Participants: Adolescents (12 to 15 years of age) from 16 schools in Jhabua and Dhar districts</p> <p>Sampling time frame: January 2015 to July 2015</p> <p>Sample size: 800</p> <p>Sex N (%):</p>	<ul style="list-style-type: none"> • Electrochemical probe method IS-3025 (Part 60). <p>Exposure level:</p> <p><u>Mean (SD) water fluoride levels</u></p> <ul style="list-style-type: none"> • Jhabua: 1.29 (± 0.52) • Dhar: 1.23 (± 0.39) • Total: 1.27 (± 0.46) 	<ul style="list-style-type: none"> • DF severity was determined using the Modified Dean Index • Examinations were conducted by trained dentists • Instruments included mouth mirror and community periodontal index probe 	<p>location, water storage method, and water fluoride content</p> <ul style="list-style-type: none"> • Statistical significance at $p < 0.05$ <p>Results:</p> <p><u>Correlation between water fluoride levels (ppm) and DF severity</u></p> <ul style="list-style-type: none"> • $r = 0.967$; $p = 0.000$ <p><u>Odds (95% CI) of DF at $>1.2\text{ppm}$ compared to $\leq 1.2\text{ppm}$</u></p> <ul style="list-style-type: none"> • OR = 1.764 (1.309, 2.377); $p < 0.0001$ 	<p>strongest predictor for dental fluorosis.” (p. 6)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Boys: 398 (49.75%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Medically compromised • Unwilling to participate • No parental consent <p>Source of funding / support:</p> <p>None that would influence the results</p> <p>Author declaration of interest:</p> <p>No COI</p>				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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)
Detection	Can we be confident in the exposure	++ Yes, exposure was measured in water using the

Risk of bias assessment				
characterization?		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 assessors would not appreciably bias

Risk of bias assessment				
				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 [\[71\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures <u>Fluoride levels in</u> • Drinking water	Outcome(s) Thyroid function	Statistical analysis: • Linear regression was used to model TSH levels as a function of urinary fluoride and iodine levels	“Adults living in Canada who have moderate-to-severe iodine deficiencies and higher levels of urinary
Study design: Cross-sectional study	• Urine	Method of outcome ascertainment		

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: Canada</p> <p>Sampling period Cycle 3 (2012 – 2013)</p> <p>Participants: Canadians (3-79) from 16 cities (CHMS)</p> <p>Sample size: 6,914,124</p> <p>Sex (%): Men: 51.54%</p> <p>Exclusions: • People living in the 3 territories, remote areas, reserves, or aboriginal</p>	<p><u>Iodine level in</u></p> <ul style="list-style-type: none"> • Urine <p>Method of exposure ascertainment</p> <p><u>Water fluoride</u> Basic anion exchange chromatography.</p> <p><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</p> <p><u>Iodine</u> Colorimetric microplate assay (using spot urine samples)</p>	<p>Serum TSH</p>	<ul style="list-style-type: none"> • Adjusting for age, sex BMI, serum calcium) <p>Results</p> <p><u>Water fluoride (mg/L)</u> Mean ±SD: 0.22 ±0.24</p> <p><u>Urinary fluoride (mg/L)</u> Mean ±SD: 0.94 ±1.05</p> <p>Change (95%CI) in serum TSH (mIU/L) per unit increase in UFsg (mg/L)</p> <p><u>No iodine deficiency</u> $\beta = -0.02 (-0.19, 0.15)$ $p = 0.43$</p> <p><u>Iodine deficiency</u> $\beta = 0.36 (-0.03, 0.75)$ $p = 0.03$</p>	<p>fluoride may be at an increased risk for underactive thyroid gland activity.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
settlements, full-time Canadian military, and institutionalized persons <ul style="list-style-type: none"> • Use of thyroid drugs • Prior thyroid diseases • Pregnancy with excess iodine levels (> 2.37 µmol/L) <p>Source of funding:</p> <ul style="list-style-type: none"> • SSHRC • CIHR • CFI • Statistics Canada <p>Conflict of interest: No COI</p>	<p>Water fluoride 0.22 mg/L ± 0.24</p> <p>Urinary fluoride 0.94 mg/L ± 1.05</p>			

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 Canadian 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)
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?	++	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 3 rd generation assay analyzer equipped with a chemiluminescent detection system. Serum free T4 was analyzed using a competitive chemiluminescent immunoassay. Thyroid hormones were analyzed at the INSPQ on the Siemens ADVIA Centaur XP analyzer. Iodine

Risk of bias assessment			
			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 [\[27\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Cross	Exposures: Fluoride levels in public drinking water supply	Outcome(s): Dental fluorosis Method of outcome	Statistical analysis: <ul style="list-style-type: none"> • Binary logistic regression Results:	“Findings indicate that the change in fluoride level from 0.7 to 0.5 ppm has reduced fluorosis and

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>sectional</p> <p>Country: Malaysia</p> <p>Participants: Lifelong residents aged 9- and 12-year-olds</p> <p>Sampling time frame: 2015 (calculated using the following information reported by the authors)</p> <ul style="list-style-type: none"> • 9-year-old children (born between 1 January and 31 December 2006) • 12-year-old children (born between 1 January and 31 December 2003) 	<p>Method of exposure assessment:</p> <p>Water fluoride: NR</p> <p>Exposure level:</p> <ul style="list-style-type: none"> • Original: 0.7 ppm • Reduced: 0.5 ppm 	<p>ascertainment:</p> <ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • "The prevalence of fluorosis (Dean's score \geq 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 ($P = 0.139$)." 	<p>maintains a caries-preventive effect. Although there is a reduction in fluorosis prevalence, the difference was not statistically significant."</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 1,143 children aged 9-12 years old</p> <p>Sex: Boys: 491 (43%)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Children who missed clinical examination. • Children with unerupted, partially unerupted or fractured incisor(s), or have a fixed orthodontic appliance. <p>Source of funding / support: Ministry of Higher</p>			<p>Fluorosis prevalence no. (%)</p> <p><u>(0) Normal</u></p> <ul style="list-style-type: none"> • Fluoridated: 342 (56.3) • Nonfluoridated: 494 (90.1) <p><u>(1) Questionable</u></p> <ul style="list-style-type: none"> • Fluoridated: 41 (6.8) • Nonfluoridated: 23 (4.2) <p><u>(2) Very mild</u></p> <ul style="list-style-type: none"> • Fluoridated: 95 (15.7) • Nonfluoridated: 23 (4.2) <p><u>(3) Mild</u></p> <ul style="list-style-type: none"> • Fluoridated: 65 (10.7) • Nonfluoridated: 5 (0.9) <p><u>(4) Moderate</u></p> <ul style="list-style-type: none"> • Fluoridated: 53 (8.7) • Nonfluoridated: 2 (0.4) 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Education, Malaysia			<p><u>(5) Severe</u></p> <ul style="list-style-type: none"> • Fluoridated:0 • Nonfluoridated: 0 <p><u>Not able to score</u></p> <ul style="list-style-type: none"> • Fluoridated:11 (1.8) • Nonfluoridated: 1 (0.2) <p><u>Total</u></p> <ul style="list-style-type: none"> • Fluoridated:607 (100.0) • Nonfluoridated: 548 (100.0) <p><u>Fluorosis (Deans > 0)</u></p> <p>Fluoridated: 254 (42.6), <i>P<0.001</i></p> <p>Nonfluoridated: 53 (9.7)</p> <p><u>Fluorosis (Deans ≥ 2)</u></p> <p>Fluoridated:213 (35.7), <i>P<0.001</i></p> <p>Nonfluoridated: 30 (5.5)</p>	
Author declaration of interest:				
No COI				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>Bivariate analysis of fluorosis prevalence with different fluoride exposures</p> <p><u>Fluorosis Deans ≥ 2</u></p> <p><i>0 ppm lifetime</i></p> <ul style="list-style-type: none"> • N (%): 30 (12.30%) • OR (95% CI), p-value: Ref. <p><i>0.5 ppm lifetime</i></p> <ul style="list-style-type: none"> • N (%): 100 (41.2%) • OR (95% CI), p-value: 8.45 (5.45-13.10), 0.001 <p><i>0.7 ppm for first 2 years and then 0.5 ppm</i></p> <ul style="list-style-type: none"> • N (%): 113 (46.5%) • OR (95% CI), p-value: 10.88 (7.03-16.84), 0.001 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>Any fluorosis: Deans > 0</u></p> <p><i>0 ppm lifetime</i></p> <ul style="list-style-type: none"> • N (%): 53 (9.7%) • OR (95% CI), p-value: Ref. <p><i>0.5 ppm lifetime</i></p> <ul style="list-style-type: none"> • N (%): 123 (40.5%) • OR (95% CI), p-value: 6.33 (4.40-9.12), 0.001 <p><i>0.7 ppm for first 2 years and then 0.5 ppm</i></p> <ul style="list-style-type: none"> • N (%): 161 (55.1%) • OR (95% CI), p-value: 7.58 (5.26-10.93), 0.001 <p>Fluorosis prevalence after fluoride concentration in the water supply was reduced</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>Fluorosis (Deans > 0)</u></p> <p><i>% Prevalence 12-year-old (PreReduction)</i></p> <ul style="list-style-type: none"> • Fluoridated: 44.6 • Nonfluoridated (control): 10.3 <p><i>% Prevalence 9-year-old (PostReduction)</i></p> <ul style="list-style-type: none"> • Fluoridated: 39.3 • Nonfluoridated (control): 8.9 <p><i>% Difference (post-pre)</i></p> <ul style="list-style-type: none"> • Fluoridated: -5.3 • Nonfluoridated (control): -1.4 <p><i>% Difference (pre)</i></p> <ul style="list-style-type: none"> • Fluoridated: 34.3 <p><i>% Difference (post)</i></p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • Fluoridated: 30.4 <p><u>Fluorosis (Deans ≥ 2)</u></p> <p><i>% Prevalence 12-year-old (PreReduction)</i></p> <ul style="list-style-type: none"> • Fluoridated: 38.4 • Nonfluoridated (control): 4.7 <p><i>% Prevalence 9-year-old (PostReduction)</i></p> <ul style="list-style-type: none"> • Fluoridated: 31.9 • Nonfluoridated (control): 6.5 <p><i>% Difference (post-pre)</i></p> <ul style="list-style-type: none"> • Fluoridated: -6.5 • Nonfluoridated (control): 1.8 <p><i>% Difference (pre)</i></p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<ul style="list-style-type: none"> • Fluoridated: 33.7 <p>% Difference (post)</p> <ul style="list-style-type: none"> • 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	
	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	N/A	Not applicable	

Risk of bias assessment			
	study groups?		
	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 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	Were all measured outcomes reported?	++	Yes, primary outcomes discussed in methods were presented in results section with adequate level of detail

Risk of bias assessment				
reporting				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 [\[72\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Ecological study	Exposure: <u>Fluoride levels in</u> <ul style="list-style-type: none"> Groundwater samples Method of exposure assessment: <ul style="list-style-type: none"> Rainy and dry season 	Outcomes: <ul style="list-style-type: none"> Schooling performance (average score and high score [$> 70\%$] prevalence) Method of outcome	Statistical analysis: <ul style="list-style-type: none"> Pearson correlation analysis was conducted Results: Ground water fluoride	<ul style="list-style-type: none"> Life-long fluoride intake from combined sources for adolescents in the United States were not strongly associated with pQCT bone measures at age

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: Sudan</p> <p>Participants: primary school students (6 to 14 years of age) residents of rural areas in Khartoum state</p> <p>Sampling time frame: NR</p> <p>Sample size (N): N = 775</p> <p>Sex:</p> <ul style="list-style-type: none"> Boys N = 315 	<p>samples were acquired from rural parts of Khartoum state</p> <ul style="list-style-type: none"> A sample of 16 groundwater wells were collected per season Analyzed “using SPADNS reagent as described by Standard Methods.” (p. 105) <p>Exposure levels:</p> <ul style="list-style-type: none"> Range for levels of fluoride in groundwater by season 	<p>ascertainment:</p> <p><u>Subjects assessed</u></p> <ul style="list-style-type: none"> Islamic studies I Islamic studies II Arabic English Mathematics Sciences History Technology <p><u>Primary examination results</u></p> <ul style="list-style-type: none"> Acquired from the Ministry of Education-Khartoum State Obtained for schools in locations sampled for groundwater 	<p><u>Dry season</u></p> <p>0.14 – 2.07 mg/L</p> <p><u>Rainy season</u></p> <p>0.01 – 1.34 mg/L</p> <ul style="list-style-type: none"> Correlation between average level of fluoride in drinking water (mg/L) and average school performance score (%) by subject <p><u>Islamic studies I</u></p> <p>r = -0.50; p = 0.008</p> <p><u>Islamic studies II</u></p> <p>r = -0.47; p = 0.013</p> <p><u>Arabic</u></p>	<p>17.</p> <ul style="list-style-type: none"> 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
Exclusions: NR Source of funding/ support: <ul style="list-style-type: none"> • 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 Author declaration of interest: NR	<u>Dry season</u> 0.14 – 2.07 mg/L <u>Rainy season</u> 0.01 – 1.34 mg/L		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 <u>Overall score</u> r = -0.51; p = 0.007	<ul style="list-style-type: none"> • Correlation between average level of

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			fluoride in drinking water (mg/L) and the prevalence of high school performance score (%) by subject <u>Islamic studies I</u> $r = -0.59; p = 0.001$ <u>Islamic studies II</u> $r = -0.35; p = 0.078$ <u>Arabic</u> $r = -0.47; p = 0.014$ <u>English</u> $r = -0.41; p = 0.034$ <u>Mathematics</u> $r = -0.39; p = 0.045$ <u>Sciences</u> $r = -0.60; p = 0.001$ <u>History</u> $r = -0.46; p = 0.016$ <u>Technology</u>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$r = -0.22; p = 0.265$ <u>Overall score</u> $r = -0.48; p = 0.012$	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 Khartoum state. The recruitment timeframe was 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?	++	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" (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	Were there no other potential threats to internal	+	Exposure was assessed at each study area. As

Risk of bias assessment				
sources	validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?			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 [\[73\]](#)

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Prospective cohort study	Exposure: <u>Period-specific daily intake of fluoride</u> <ul style="list-style-type: none"> • Birth to 8.5 years • 8.5 to 14 years • 14 to 17 years • Birth to 17 years <u>Cumulative average</u>	Outcomes: <u>Radial and tibial bone characteristics</u> <ul style="list-style-type: none"> • Cortical content • Cortical density • Trabecular content • Trabecular density • Compression strength 	Statistical analysis: <ul style="list-style-type: none"> • Multivariate regression models were used • Models were adjusted for height, weight, calcium and protein intake, time since 	<ul style="list-style-type: none"> • “In summary, the findings show that the effects of life-long fluoride intake from combined sources for adolescents in the United States were not strongly associated with pQCT

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: USA</p> <p>Participants: Adolescents (17 years of age) whose families were recruited into the Iowa Fluoride Study (IFS) from hospitals following birth</p> <p>Sampling time frame: <u>IFS:</u> 1992 to 1995 <u>Iowa Bone Development Study (IBDS) – IFS Subset</u> 1998 to 2000</p>	<p><u>daily intake of fluoride</u></p> <ul style="list-style-type: none"> • Birth to 17 years <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 then every 6 months up to age 17 years.” (p. 5) • Sources of exposure 	<ul style="list-style-type: none"> • Torsion strength <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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 technicians (N = 2) who were certified 	<p>peak height velocity (PHV), and physical activity.</p> <ul style="list-style-type: none"> • Results were considered significant at $p < 0.01$ • Results were considered suggestive at $0.01 < p < 0.05$ <p>Results: RADIAL BONE - GIRLS</p> <ul style="list-style-type: none"> • Change (SE) in trabecular content (mg) per 1 mg unit increase in daily fluoride intake during the specified time 	<p>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)</p>

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Sample size (N): 380 Sex (N): <ul style="list-style-type: none"> Boys N = 176 Exclusions: NR Source of funding/ support: <ul style="list-style-type: none"> NIH grants Wright-Bush Shreves Endowed Professor Fund University of Iowa Author declaration of	assessed include "... water, other beverages, selected foods, dietary fluoride supplements, and ingested fluoride toothpaste ..." (p. 4) <ul style="list-style-type: none"> 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 	with the International Society of Clinical Densitometry (ISCD) <ul style="list-style-type: none"> "The non-weight bearing, non-dominant arm, and the weight-bearing left leg were selected for imaging." (p. 4) 	period among girls <u>0 to 8.5 years (N = 140)</u> $\beta = -2.60 (2.53)$ $p = 0.31$ <u>8.5 to 14 years (N = 125)</u> $\beta = -0.15 (2.21)$ $p = 0.95$ <u>14 to 17 years (N = 122)</u> $\beta = 0.09 (1.84)$ $p = 0.96$ <u>0 to 17 years (N = 112)</u> $\beta = 0.59 (3.30)$ $p = 0.86$ <ul style="list-style-type: none"> Change (SE) in trabecular density 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
interest: NR	<p>Exposure levels:</p> <ul style="list-style-type: none"> • Range for level of fluoride intake <p>Women: 0.7 - 0.8 mg /day</p> <p>Men: 0.7 - 0.9 mg /day.</p>		<p>(mg/cm³) per 1 mg unit increase in daily fluoride intake during the specified time period among girls</p> <p><u>0 to 8.5 years (N = 140)</u></p> <p>$\beta = 2.22$ (9.50)</p> <p>$p = 0.82$</p> <p><u>8.5 to 14 years (N = 125)</u></p> <p>$\beta = -3.79$ (8.08)</p> <p>$p = 0.64$</p> <p><u>14 to 17 years (N = 122)</u></p> <p>$\beta = 3.70$ (6.59)</p> <p>$p = 0.58$</p> <p><u>0 to 17 years (N = 112)</u></p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 0.99$ (12.14) $p = 0.94$ <ul style="list-style-type: none"> • 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> $\beta = -5.79$ (2.54) $p = 0.03$ <u>8.5 to 14 years (N = 125)</u> $\beta = -0.74$ (2.19) $p = 0.74$ <u>14 to 17 years (N = 122)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -1.19 (1.76)$ $p = 0.50$ <u>0 to 17 years (N = 112)</u> $\beta = -3.19 (3.33)$ $p = 0.34$ <ul style="list-style-type: none"> • Change (SE) in cortical density (mg/cm³) 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> $\beta = 5.30 (4.44)$ $p = 0.24$ <u>8.5 to 14 years (N = 125)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -4.30$ (3.63) $p = 0.24$ <u>14 to 17 years (N = 122)</u> $\beta = 0.42$ (3.05) $p = 0.89$ <u>0 to 17 years (N = 112)</u> $\beta = -2.28$ (5.46) $p = 0.68$ <ul style="list-style-type: none"> • 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>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -1.08 (2.42)$ $p = 0.66$ <u>8.5 to 14 year (N = 125)</u> $\beta = -1.21 (2.12)$ $p = 0.57$ <u>14 to 17 years (N = 122)</u> $\beta = 0.09 (1.76)$ $p = 0.96$ <u>0 to 17 years (N = 112)</u> $\beta = -2.00 (3.10)$ $p = 0.52$	
			<ul style="list-style-type: none"> • Change (SE) in torsion strength (mm³) per 1 mg unit increase in daily fluoride intake during the specified 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			time period among girls <u>0 to 8.5 years (N = 140)</u> $\beta = -31.42 (12.28)$ $p = 0.02$ <u>8.5 to 14 years (N = 125)</u> $\beta = -3.76 (9.95)$ $p = 0.71$ <u>14 to 17 years (N = 122)</u> $\beta = -7.34 (7.73)$ $p = 0.35$ <u>0 to 17 years (N = 112)</u> $\beta = -21.00 (14.95)$ $p = 0.17$	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>RADIAL BONE - BOYS</p> <ul style="list-style-type: none"> • Change (SE) in trabecular content (mg) per 1 mg unit increase in daily fluoride intake during the specified time period among boys <p><u>0 to 8.5 years (N = 125)</u></p> <p>$\beta = -4.83 (3.85)$ $p = 0.21$</p> <p><u>8.5 to 14 years (N = 112)</u></p> <p>$\beta = -1.79 (3.52)$ $p = 0.61$</p> <p><u>14 to 17 years (N = 115)</u></p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 1.41 (2.57)$ $p = 0.59$ <u>0 to 17 years (N = 105)</u> $\beta = -5.63 (4.28)$ $p = 0.19$ <ul style="list-style-type: none"> • Change (SE) in trabecular density (mg/cm^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> $\beta = 0.36 (10.77)$ $p = 0.98$ <u>8.5 to 14 years (N = 112)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -3.36$ (9.22) $p = 0.72$ <u>14 to 17 years (N = 115)</u> $\beta = 1.27$ (7.00) $p = 0.86$ <u>0 to 17 years (N = 105)</u> $\beta = -7.88$ (11.51) $p = 0.50$ <ul style="list-style-type: none"> • Change (SE) in cortical 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 = 125)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 2.94 (4.04)$ $p = 0.47$ <u>8.5 to 14 years (N = 112)</u> $\beta = -0.36 (3.49)$ $p = 0.92$ <u>14 to 17 years (N = 115)</u> $\beta = 1.82 (2.63)$ $p = 0.49$ <u>0 to 17 years (N = 105)</u> $\beta = 0.37 (4.10)$ $p = 0.93$ <ul style="list-style-type: none"> • Change (SE) in cortical density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>the specified time period among boys</p> <p><u>0 to 8.5 years (N = 125)</u></p> <p>$\beta = 11.64 (6.09)$</p> <p>$p = 0.06$</p> <p><u>8.5 to 14 years (N = 112)</u></p> <p>$\beta = 0.92 (4.94)$</p> <p>$p = 0.86$</p> <p><u>14 to 17 years (N = 115)</u></p> <p>$\beta = -0.51 (3.73)$</p> <p>$p = 0.90$</p> <p><u>0 to 17 years (N = 105)</u></p> <p>$\beta = -0.21 (6.16)$</p> <p>$p = 0.98$</p> <p>• Change (SE) in</p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>compression strength (mg^2/mm^4) per 1 mg unit increase in daily fluoride intake during the specified time period among boys</p> <p><u>0 to 8.5 years (N = 125)</u></p> <p>$\beta = 2.70$ (4.29) $p = 0.53$</p> <p><u>8.5 to 14 years (N = 112)</u></p> <p>$\beta = -0.79$ (3.65) $p = 0.83$</p> <p><u>14 to 17 years (N = 115)</u></p> <p>$\beta = 1.83$ (2.80) $p = 0.52$</p> <p><u>0 to 17 years (105)</u></p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 0.72 (4.43)$ $p = 0.88$ <ul style="list-style-type: none"> • 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> $\beta = -1.08 (19.57)$ $p = 0.96$ <u>8.5 to 14 years (N = 112)</u> $\beta = -2.02 (16.68)$ $p = 0.91$ <u>14 to 17 years (N = 115)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 14.60$ (12.40) $p = 0.24$ <u>0 to 17 years (N = 105)</u> $\beta = 8.05$ (19.62) $p = 0.69$	
			<p>TIBIAL BONE - GIRLS</p> <ul style="list-style-type: none"> • Change (SE) in trabecular 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 = 136)</u> $\beta = 2.77$ (7.78)	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>$p = 0.73$</p> <p><u>8.5 to 14 years (N = 121)</u></p> <p>$\beta = 2.86 (6.37)$</p> <p>$p = 0.66$</p> <p><u>14 to 17 years (N = 119)</u></p> <p>$\beta = -0.25 (5.60)$</p> <p>$p = 0.97$</p> <p><u>0 to 17 years (N = 109)</u></p> <p>$\beta = 0.24 (10.07)$</p> <p>$p = 0.98$</p> <ul style="list-style-type: none"> • Change (SE) in trabecular density (mg/cm^3) per 1 mg unit increase in daily fluoride intake during the specified time 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			period among girls <u>0 to 8.5 years (N = 136)</u> $\beta = 0.38$ (9.28) $p = 0.97$ <u>8.5 to 14 years (N = 121)</u> $\beta = -1.97$ (7.70) $p = 0.80$ <u>14 to 17 years (N = 119)</u> $\beta = 1.24$ (6.10) $p = 0.84$ <u>0 to 17 years (N = 109)</u> $\beta = -8.66$ (11.63) $p = 0.46$ • Change (SE) in cortical content (mg)	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			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> $\beta = -11.97 (9.97)$ $p = 0.23$ <u>8.5 to 14 years (N = 121)</u> $\beta = 14.18 (8.01)$ $p = 0.08$ <u>14 to 17 years (N = 119)</u> $\beta = 11.49 (6.25)$ $p = 0.07$ <u>0 to 17 years (N = 109)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 14.24$ (11.95) $p = 0.24$ <ul style="list-style-type: none"> • Change (SE) in cortical density (mg/cm^3) 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> $\beta = 6.44$ (4.91) $p = 0.19$ <u>8.5 to 14 years (N = 121)</u> $\beta = -6.64$ (3.84) $p = 0.09$ <u>14 to 17 years (N = 119)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -1.11 (3.10)$ $p = 0.72$ <u>0 to 17 years (N = 109)</u> $\beta = -0.86 (6.07)$ $p = 0.89$ <ul style="list-style-type: none"> • 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> $\beta = -5.39 (5.56)$ $p = 0.34$ <u>8.5 to 14 years (N = 121)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 0.96$ (4.67) $p = 0.84$ <u>14 to 17 years (N = 119)</u> $\beta = 3.17$ (3.72) $p = 0.40$ <u>0 to 17 years (N = 109)</u> $\beta = -1.62$ (6.82) $p = 0.82$ <ul style="list-style-type: none"> • Change (SE) in torsion strength (mm³) 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>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -111.79$ (60.22) $p = 0.07$ <u>8.5 to 14 years (N = 121)</u> $\beta = 111.99$ (49.32) $p = 0.03$ <u>14 to 17 years (N = 119)</u> $\beta = 44.73$ (38.60) $p = 0.25$ <u>0 to 17 years (N = 109)</u> $\beta = 64.15$ (74.10) $p = 0.39$	
			TIBIAL BONE - BOYS <ul style="list-style-type: none"> • Change (SE) in trabecular content 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			(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> $\beta = -1.95$ (9.08) $p = 0.84$ <u>8.5 to 14 years (N = 111)</u> $\beta = 0.02$ (7.82) $p = 0.99$ <u>14 to 17 years (N = 114)</u> $\beta = 9.77$ (5.84) $p = 0.10$ <u>0 to 17 years (N = 104)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = -5.82 (9.37)$ $p = 0.54$ <ul style="list-style-type: none"> • Change (SE) in trabecular density (mg/cm^3) 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> $\beta = 9.91 (9.63)$ $p = 0.31$ <u>8.5 to 14 years (N = 111)</u> $\beta = 2.65 (8.43)$ $p = 0.76$ <u>14 to 17 years (N = 114)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 6.64 (6.32)$ $p = 0.30$ <u>0 to 17 years (N = 104)</u> $\beta = 7.31 (10.37)$ $p = 0.49$ <ul style="list-style-type: none"> • Change (SE) in cortical 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> $\beta = 13.74 (13.05)$ $p = 0.30$ <u>8.5 to 14 years (N = 111)</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 13.18 (11.40)$ $p = 0.25$ <u>14 to 17 years (N = 114)</u>	
			$\beta = 21.40 (8.38)$ $p = <0.01$ <u>0 to 17 years (N = 104)</u>	
			$\beta = 16.19 (13.63)$ $p = 0.24$ <ul style="list-style-type: none"> • Change (SE) in cortical density (mg/cm^3) 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>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			$\beta = 7.37 (5.50)$ $p = 0.19$ <u>8.5 to 14 years (N = 111)</u> $\beta = -7.16 (4.37)$ $p = 0.11$ <u>14 to 17 years (N = 114)</u> $\beta = -3.52 (3.46)$ $p = 0.31$ <u>0 to 17 years (N = 104)</u> $\beta = -0.06 (5.52)$ $p = 0.99$	
			<ul style="list-style-type: none"> • Change (SE) in compression strength (mg^2/mm^4) per 1 mg unit increase in daily fluoride intake during 	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>the specified time period among boys</p> <p><u>0 to 8.5 years (N = 124)</u></p> <p>$\beta = 10.96 (7.81)$</p> <p>$p = 0.17$</p> <p><u>8.5 to 14 years (N = 111)</u></p> <p>$\beta = 7.53 (6.92)$</p> <p>$p = 0.28$</p> <p><u>14 to 17 years (N = 114)</u></p> <p>$\beta = 10.58 (5.22)$</p> <p>$p = 0.05$</p> <p><u>0 to 17 years (N = 104)</u></p> <p>$\beta = 9.37 (8.34)$</p> <p>$p = 0.27$</p> <p>• Change (SE) in</p>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			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 = 124)</u> $\beta = 93.65$ (87.79) $p = 0.29$ <u>8.5 to 14 years (N = 111)</u> $\beta = 72.06$ (74.95) $p = 0.34$ <u>14 to 17 years (N = 114)</u> $\beta = 175.06$ (56.42) $p = <0.01$ <u>0 to 17 years (N =</u>	

Study characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			104) $\beta = 90.24$ (95.28) $p = 0.35$	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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.
Confounding	Did the study design or analysis account for	++	Multivariable regression models were adjusted for height, weight, time since PHV [Peak Height Velocity],

Risk of bias assessment			
	important confounding and modifying variables?		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?	++	<p>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.</p> <p>[a] 20% lower sample size resulted when calcium, protein, and physical activity were added to the model due to missing data."</p> <p>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, with endpoints allowed to be interpolated from estimates within 7 months of the stated endpoints. The</p>

Risk of bias assessment			
			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 possesses several limitations in terms of its reliability and validity.
	Can we be confident in the outcome	++	Participants were followed from birth to 17 years of age. Trabecular and cortical bone characteristics of

Risk of bias assessment			
	assessment?		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.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original pilot study</p> <p>Study design: Case-control (Only cross-sectional analysis results relevant to the review are included)</p> <p>Country: India</p> <p>Participants: Children (4 to 12 years of age) with nephrotic</p>	<p>Exposure: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Urine samples • Serum samples <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Measured using potentiometric method with fluoride selective ion electrode <p>Exposure levels: Urinary fluoride,</p>	<p>Outcomes: <u>Nephrotoxicity:</u></p> <ul style="list-style-type: none"> • Renal tubule ultrastructural changes • Renal tubule apoptosis <p>Method of outcome ascertainment: <u>Renal biopsy</u></p> <ul style="list-style-type: none"> • Suggested for G-1 and G-2 participants who had kidneys of 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 <p>Results: <u>Ultrastructural changes</u></p> <ul style="list-style-type: none"> • TEM images showed accumulation of 	<ul style="list-style-type: none"> • 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

²⁸ 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
<p>syndrome minimal change disease (NS-MCD) from All India Institute of Medical Sciences' department for pediatric outpatients</p> <p>Sampling time frame: June 2012 - January 2015</p> <p>Sample size (N): 156</p> <p><u>Group 1 (G-1): Nephrotic syndrome patients (NSP) with normal fluoride levels in urine (≤ 1 ppm)</u></p>	<p>mean \pmSD</p> <ul style="list-style-type: none"> • Gp 0: 0.56 ppm \pm0.15 • Gp 1: 0.61 ppm \pm0.17 • Gp 2: 4.01 ppm \pm1.83 <p>Serum fluoride, mean \pmSD</p> <ul style="list-style-type: none"> • Gp 0: 0.07 ppm \pm11 • Gp 1: 0.07 ppm \pm0.01 • Gp 2: 0.1 ppm \pm0.013 <ul style="list-style-type: none"> • 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 	<p>regular size with no blockage and proteinuria, but the cause was unknown</p> <ul style="list-style-type: none"> • Ultrasounds were used to guide the procedure • Biopsy gun was used to acquire kidney tissues • A nephrologist and/or interventional radiologist conducted the procedure <p><u>Ultrastructural changes of kidney tissues</u></p> <ul style="list-style-type: none"> • Transition electron microscopy (TEM) <p><u>Renal tubule apoptosis</u></p>	<p>multiple dark spherical microparticles within the tubular basement membranes... and basement membrane disintegration... in Gp 2</p> <ul style="list-style-type: none"> • 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. 	<p>vacuolation, nuclear condensation, apoptosis, and necrosis, were observed.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • N = 32 <u>Group 2 (G-2): NSP with high fluoride levels in urine (> 1 ppm)</u> <ul style="list-style-type: none"> • N = 32 <u>Group 0 (G-0): Healthy controls matched by age with normal fluoride levels in urine (≤ 1 ppm)</u> <ul style="list-style-type: none"> • N = 32 <p>Sex: NR</p> <p>Exclusions: NR</p> <p>Source of funding/</p>	<p>level of fluoride in serum was reported among participants in G-2 than those in G-1 and G-0 (p = 0.001)</p>	<ul style="list-style-type: none"> • Terminal deoxynucleotidyl transferase deoxyuridine triphosphate (dUTP) nick end labeling (TUNEL) assay 	<ul style="list-style-type: none"> • 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. <p><u>Renal tubule apoptosis</u></p> <ul style="list-style-type: none"> • Level of renal tubule apoptosis among participants in G-1 and G2 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
support: None Author declaration of interest: None			G-1 = 7% G-2 = 22% p = 0.001	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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' department of pediatric outpatients. The study period was from June 2012 to January 2015. Each study group has the same number of participants.

Risk of bias assessment			
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 triphosphate nick end labelling, respectively. Blinding status unlikely to affect outcome assessment.
Selective	Were all measured outcomes reported?	+	Ultrastructural changes in kidney tissues and

Risk of bias assessment			
reporting			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 [\[75\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original Study	Exposures: <u>Fluoride levels in</u> • Drinking water samples • Urine samples	Outcomes: <u>Thyroid hormone derangement</u> • Serum levels of free T4 (FT4), free T3	Statistical analysis: NR Results:	• When serum FT3, FT4 and TSH of different category of our study were compared we found

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Cross-sectional study</p> <p>Country: India</p> <p>Participants: Children (8 to 14 years of age) from Jodhpur district villages of Rajasthan</p> <p>Sampling time frame: NR</p> <p>Sample size (N): 100</p> <p>• N = 25 per exposure group</p>	<p>• Blood samples</p> <p>Method of exposure assessment:</p> <p><u>Drinking water samples:</u></p> <p>• Electrochemical method</p> <p><u>Urine and blood samples</u></p> <p>• F ion specific electrode</p> <p><u>Exposure groups</u></p> <p>• Villages were categorized based on fluoride levels in drinking water, yielding the following</p>	<p>(FT3), and thyroid stimulating hormone (TSH)</p> <p>Method of outcome ascertainment:</p> <p>• Chemiluminescence Assay</p>	<p>• Free T3: mean, \pmSD, [range] (pg/mL)</p> <p><u>Gp 1:</u> 2.66 pg/mL \pm0.46, [2.11 – 3.89]</p> <p><u>Gp 2:</u> 2.73 pg/mL \pm0.36, [2.13 – 3.56]</p> <p><u>Gp 3:</u> 2.84 pg/mL \pm0.46, [2.02 – 4.26]</p> <p><u>Gp 4:</u> 3.06 pg/mL \pm0.78, [1.91 – 4.42]</p> <p>• Free T4: mean \pmSD, [range] (ng/dL)</p> <p><u>Gp 1:</u> 0.98 \pm0.21, [0.79 – 1.79]</p> <p><u>Gp 2:</u> 1.02 \pm0.26, [0.78 – 1.89]</p> <p><u>Gp 3:</u> 1.11 \pm0.28, [0.76 – 1.98]</p> <p><u>Gp 4:</u> 1.22 \pm 0.33,</p>	<p>significant difference between these.</p> <p>• 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.</p> <p>• 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</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sex: NR</p> <p>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, medically and physically compromised patients...” (p. 328)</p>	<p>exposure groups:</p> <p>Gp 1: <1ppm</p> <p>Gp 2: 1-1.9 ppm</p> <p>Gp 3: 2-3.9 ppm</p> <p>Gp 4: ≥ 4ppm</p> <p>Exposure levels:</p> <ul style="list-style-type: none"> • Urinary fluoride, mean ±SD <ul style="list-style-type: none"> ○ 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 		<p>[0.75 – 1.89]</p> <p>• TSH: Mean ± SD, [range] (µIU/mL)</p> <p><u>Gp 1:</u> 1.33 ±0.78, [0.4 – 2.99]</p> <p><u>Gp 2:</u> 1.64 ±0.88), [0.29 – 3.76]</p> <p><u>Gp 3:</u> 1.86 ±0.77, [0.76 – 3.74]</p> <p><u>Gp 4:</u> 1.91 ±1.10, [0.75 – 4.99]</p>	<p>other studies.</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Source of funding/ support: NR	<ul style="list-style-type: none"> ○ Gp 1: 0.046 mg/L ±0.02 			
Author declaration of interest: NR	<ul style="list-style-type: none"> ○ 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
	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 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).
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.

Risk of bias assessment			
	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 [\[76\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposure: <u>Fluoride levels in</u> • Drinking water samples	Outcomes: Non-skeletal manifestations of fluoride toxicity	Statistical analysis: Frequency between study groups	• Higher proportion of study subjects with clinical manifestations of non-skeletal

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional study</p> <p>Country: India</p> <p>Participants: Individuals living in randomly selected villages of Bangarpet taluk, Kolar. Study groups are comprised of areas with high (Thimmasandra and Batwarahalli) and normal (Maddinayakanahalli) levels of fluoride in water. The median</p>	<p>Method of exposure assessment:</p> <ul style="list-style-type: none"> 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) <p>Exposure levels: <u>High fluoride group</u> > 1.5 mg/L fluoride in water</p>	<p>Method of outcome ascertainment: <u>Evaluated using clinical history for the following:</u></p> <ul style="list-style-type: none"> Dyspepsia with nausea, vomiting, abdomen pain, constipation, or diarrhea Muscle weakness Tiredness Fatigue Polyuria Polydipsia Recurrent abortions or stillbirths 	<p>Result:</p> <ul style="list-style-type: none"> Number (%) of participants with non-skeletal manifestations of fluorosis by study groups <p><u>Dyspepsia = 32 (100.0)</u></p> <p>High fluoride group = 24 (75.0)</p> <p>Normal fluoride group = 8 (25.0)</p> <p><u>Muscle weakness = 13 (100.0)</u></p> <p>High fluoride group = 9 (69.23)</p>	<p>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.</p> <ul style="list-style-type: none"> 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
<p>(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.</p> <p>Sampling time frame: Study duration of 1 year</p> <p>Sample size (N): <u>High fluoride group</u> • N = 486 <u>Normal fluoride group</u> • N = 417</p>	<p><u>Normal fluoride group</u> < 1.0 mg/L fluoride in water</p>		<p>Normal fluoride group = 4 (30.77)</p> <p><u>Fatigue = 32 (100.0)</u></p> <p>High fluoride group = 19 (59.38)</p> <p>Normal fluoride group = 13 (40.62)</p> <p>•“None of the study participants had complaints of polyuria, polydipsia, repeated abortions, and repeated stillbirths...” (p. 1225)</p> <p>•“The study subjects</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sex:</p> <p><u>High fluoride group</u></p> <ul style="list-style-type: none"> • Men N (%): 245 (55.1) <p><u>Normal fluoride group</u></p> <ul style="list-style-type: none"> • Men (%) = 200 (44.9) <p>Exclusions:</p> <ul style="list-style-type: none"> • Has no teeth, • Has artificial teeth • Is pregnant • Is bedridden • Is not available following the second visit <p>Source of funding/</p>			<p>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)</p>	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>support:</p> <p>None</p> <p>Author declaration of interest:</p> <p>None</p>				

Risk of bias assessment

<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 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

Risk of bias assessment			
			(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.
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	–	Clinical history of select conditions were used to determine non-skeletal fluorosis manifestations.

Risk of bias assessment			
	assessment?		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 [\[77\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u> • Urine samples • Drinking water	Outcomes: • Intelligence quotient (IQ)	Statistical analysis: • Piecewise linear regression and multiple logistic regression models	• “In our study, urinary fluoride levels presented a positive relationship with water fluoride concentration,

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Cross-sectional study</p> <p>Country: China</p> <p>Participants: Random sample of children (7 to 13 years of age) from rural areas of Tianjin city with high and normal levels of fluoride</p> <p>Sampling time frame: 2015</p> <p>Sample size (N): 2,886</p> <p><u>Normal-fluoride exposure (water</u></p>	<p>samples</p> <p>Method of exposure assessment:</p> <p><u>Water samples</u></p> <ul style="list-style-type: none"> • Public water supplies were randomly sampled per village (N = 168) • Measured using the national standardized ion selective electrode method <p><u>Urine samples:</u></p> <ul style="list-style-type: none"> • Early morning spot urine samples were acquired from participants (N = 	<p>Method of outcome ascertainment:</p> <p><u>Second edition of the Combined Raven's Test – The Rural in China (CRT-RC2)</u></p> <ul style="list-style-type: none"> • Used to determine IQ scores which was grouped as: <ul style="list-style-type: none"> Retarded: ≤ 69 Marginal: 70 – 79 Dull normal: 80 – 89 Normal: 90 – 109 High normal: 110 – 119 Superior: 120 – 129 Excellent: ≥ 130 • The validated test was independently 	<p>were used to assess associations of interest</p> <ul style="list-style-type: none"> • Stepwise linear regression models used to identify possible confounders • Models were adjusted for age, sex, paternal education, maternal education, and low birth weight <p>Results:</p> <ul style="list-style-type: none"> • Threshold effect analysis: Change (95% CI) in IQ scores per 0.5 mg/L increment of fluoride 	<p>indicating that fluoride from drinking water makes important contribution to urinary fluoride.” (p. 120)</p> <ul style="list-style-type: none"> • “...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)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p><u>fluoride ≤ 1.0 mg/L</u></p> <ul style="list-style-type: none"> • N = 1,636 <p><u>High-fluoride exposure</u> (water fluoride > 1.0 mg/L)</p> <ul style="list-style-type: none"> • N = 1,250 <p>Sex:</p> <p><u>Normal-fluoride exposure</u></p> <ul style="list-style-type: none"> • Boys N (%): 849 (51.9) <p><u>High-fluoride exposure</u></p> <ul style="list-style-type: none"> • Boys N (%): 667 (53.4) <p>Exclusions:</p>	<p>2,380)</p> <ul style="list-style-type: none"> • Measured using the national standardized ion selective electrode method <p>Exposure levels:</p> <ul style="list-style-type: none"> • Mean (SD) levels of fluoride in water (mg/L) (p <0.001) <p><u>Normal-fluoride exposure</u></p> <p>0.50 (0.27)</p> <p><u>High-fluoride exposure</u></p> <p>2.00 (0.75)</p> <ul style="list-style-type: none"> • Mean (SD) levels of fluoride in urine 	<p>completed by participants within 40 minutes and this was overseen by four trained professionals</p>	<p>in water by concentration ranges</p> <p><u>0.20 – 3.40 mg/L</u></p> <p>β = -0.04 (- 0.33, 0.24)</p> <p><u>3.40 – 3.90 mg/L</u></p> <p>β = - 4.29 (- 8.09, - 0.48)</p> <ul style="list-style-type: none"> • Threshold effect analysis: Change (95% CI) in IQ scores per 0.5 mg/L increment of fluoride in urine by concentration ranges <p><u>0.01 – 1.60 mg/L</u></p> <p>β = 0.36 (- 0.29, 1.01)</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Were not lifetime residents of the study area 	(mg/L) (p <0.001) <u>Normal-fluoride exposure</u>		<u>1.60 – 2.50 mg/L</u> $\beta = -2.67 (-4.67, -0.68)$	
<ul style="list-style-type: none"> • Has a disease that impacts intelligence (congenital or acquired) 	0.41 (0.49) <u>High-fluoride exposure</u> 1.37 (1.08)		<u>2.50 – 5.54 mg/L</u> $\beta = -0.84 (-2.18, 0.50)$	
<ul style="list-style-type: none"> • Has history of cerebral trauma or neurological disorders • Has history of a positive screening test for Down's syndrome or hepatitis B/treponema palladium infection 				<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Gestational exposure to maternal smoking • Gestational exposure 			<u>Excellent IQ</u> $OR = 0.47 (0.32, 0.71)$	
			<u>Superior IQ</u>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>to maternal drinking</p> <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • State Key Program of National Natural Science of China, and the Fundamental Research Funds for the Central Universities <p>Author declaration of interest: None</p>			<p>OR = 0.89 (0.69, 1.15)</p> <p><u>High normal IQ</u></p> <p>OR = 0.96 (0.80, 1.15)</p> <p><u>Dull normal IQ</u></p> <p>OR = 0.85 (0.62, 1.17)</p> <p><u>Marginal IQ</u></p> <p>OR = 1.25 (0.69, 2.26)</p> <ul style="list-style-type: none"> • 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 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<u>Excellent IQ</u> OR = 0.49 (0.26, 0.93)	
			<u>Superior IQ</u> 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)	
			<ul style="list-style-type: none"> • Stratified threshold effect analysis: Odds (95% CI) of IQ level 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			per 0.5 mg/L increment of fluoride in water; normal IQ is the control <u>Excellent IQ (Fluoride level of 0.20 – 1.40 mg/L)</u> OR = 0.60 (0.47, 0.77) <u>Excellent IQ (Fluoride level of 1.40 – 3.90 mg/L)</u> OR = 1.09 (0.88, 1.36) <u>Superior IQ</u> OR = 0.99 (0.93, 1.06) <u>High normal IQ</u> OR = 0.98 (0.94, 1.03)	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p><u>Dull normal IQ</u></p> <p>OR = 0.96 (0.88, 1.05)</p> <p><u>Marginal IQ</u></p> <p>OR = 1.04 (0.89, 1.23)</p> <p>• 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</p> <p><u>Excellent IQ</u></p> <p>OR = 0.87 (0.76, 1.01)</p> <p><u>Superior IQ</u></p> <p>OR = 0.96 (0.89,</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			1.04) <u>High normal IQ</u> OR = 0.99 (0.94, 1.04) <u>Dull normal IQ</u> OR = 0.90 (0.81, 1.00) <u>Marginal IQ</u> OR = 1.07 (0.91, 1.25)	

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

Risk of bias assessment			
	concealed?		
	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 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.

Risk of bias assessment			
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 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.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Case-control (Only cross-sectional analysis results are relevant to current review)</p> <p>Country: India</p> <p>Participants:</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Serum <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Venipuncture used to collect samples of overnight fasting blood • Measured using Orion Ion Analyser <p>Exposure level:</p>	<p>Outcomes:</p> <p><u>Degree of lipid peroxidation</u></p> <ul style="list-style-type: none"> • Plasma thiobarbituric acid reactive substance (TBARS) • Erythrocyte TBARS <p><u>Lipid profiles</u></p> <ul style="list-style-type: none"> • Cholesterol • Triglyceride (TGL) • High-density lipoprotein (HDL) • LDL • VLDL 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • Pearson’s correlation was used • Correlations at level of 0.05 and 0.01 (2-tailed) were identified as significant <p>Results:</p> <p>Correlation between serum fluoride and outcomes in patients with fluorosis</p> <ul style="list-style-type: none"> • <u>Plasma TBARS</u> r = 0.095; p = 0.019 	<ul style="list-style-type: none"> • 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,

²⁹ 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
<p>Fluorosis (dental and skeletal) cases and controls from 3 Tamil Nadu districts with high levels of fluoride in water (Salem, Dharmapuri, and Krishnagiri)</p> <p>Sampling time frame: NR</p> <p>Sample size (N): 508</p> <p><u>Group I (controls)</u></p> <ul style="list-style-type: none"> • N = 52 <p><u>Group II (mild fluorosis)</u></p> <ul style="list-style-type: none"> • N = 112 	<ul style="list-style-type: none"> • Drinking water fluoride concentration: > 1.5 mg/l • Mean (SD) level of fluoride (mg/L) in serum by study groups <p><u>Group I (controls):</u> 0.07 (0.08)</p> <p><u>Group II (mild fluorosis):</u> 0.13 (0.02)</p> <p><u>Group III (moderate fluorosis):</u> 0.19 (0.03)</p> <p><u>Group IV (severe fluorosis):</u></p>	<p><u>Enzyme activity</u></p> <ul style="list-style-type: none"> • Paraoxonase (PON1) • Arylesterase (ARE) • Lactonase <p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Venipuncture used to collect samples of overnight fasting blood • Biochemical assays conducted at ≤ 2 days from sample collection <p><u>Erythrocyte and plasma TBARS</u></p> <ul style="list-style-type: none"> • Creatinine kinase (CK-MB) assay 	<ul style="list-style-type: none"> • <u>Erythrocyte TBARS</u> r = 0.783; p = 0.000 • <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 	<p>which support the chances of cardiovascular related complications in fluorosis patients.</p> <ul style="list-style-type: none"> • 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 of serum fluoride levels with PON1, ARE, and lactonase. • No significant association of serum

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p><u>Group III (moderate fluorosis)</u></p> <ul style="list-style-type: none"> • N = 136 <p><u>Group IV (severe fluorosis)</u></p> <ul style="list-style-type: none"> • N = 208 <p>Sex (N):</p> <p><u>Group I (controls)</u></p> <ul style="list-style-type: none"> • Men = 28; Women = 24 <p><u>Group II (mild fluorosis)</u></p> <ul style="list-style-type: none"> • Men = 76; Women = 36 <p><u>Group III (moderate fluorosis)</u></p> <ul style="list-style-type: none"> • Men = 78; Women = 	<p>0.28 (0.03)</p>	<ul style="list-style-type: none"> • Used to evaluate fluoride toxicity by identifying lipid peroxidation products <p><u>TGL and HDL</u></p> <ul style="list-style-type: none"> • AGAPPE diagnostic kit <p><u>Other parameters of blood</u></p> <ul style="list-style-type: none"> • Standard protocols <p><u>PON1</u></p> <ul style="list-style-type: none"> • p-nitrophenol released at 412 nm used to determine enzyme activity <p><u>ARE</u></p> <ul style="list-style-type: none"> • Enzyme activity determined using 	<p>Activity of membrane bound and pesticide scavenging enzymes in fluorosis patients.</p> <p><u>Serum level of AChE (U/l)</u></p> <ul style="list-style-type: none"> • Controls: 6.29 ± 0.68 • Mild: 4.64 ± 0.54 • Moderate: 4.11 ± 0.4 • Severe: 3.78 ± 0.35 <p><u>Serum level of ATPase/Na+ K+ ATPase</u></p> <ul style="list-style-type: none"> • Controls: 2.41 ± 0.34 • Mild: 2.56 ± 0.31 • Moderate: 2.64 ± 0.29 • Severe: 2.87 ± 0.4 	<p>fluoride levels with TGL and VLDL.</p> <ul style="list-style-type: none"> • 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 prolonged fluoride ingestion (observed in moderate and severe

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>58</p> <p><u>Group IV (severe fluorosis)</u></p> <ul style="list-style-type: none"> Men = 112; Women = 96 <p>Exclusions:</p> <ul style="list-style-type: none"> “...smoking, heart, liver/kidney disease, cancer, chronic inflammation, autoimmune and hematological disorders.” (p. 207) <p>Source of funding/ support:</p> <p>Periyar University, and</p>		<p>absorbance of phenylacetate at 270 nm</p> <p><u>Lactonase activity</u></p> <ul style="list-style-type: none"> UV-visible spectrophotometer used to determine absorbance at 270 nm <p><u>Serum level of AChE and ATPase/Na+ K+ ATPase</u></p> <ul style="list-style-type: none"> AChE: described by Ellman et al. [17] ATPase: measured by estimating the liberated inorganic phosphorus (Pi), after the reaction of 		<p>groups) caused continuous multifaceted calamities beyond the regenerative capacity of the liver tissues.</p> <ul style="list-style-type: none"> Furthermore, the decreased activity of the erythrocyte membrane bound enzymes, AChE and ATPase indicates the prevalence of memory loss with lower IQ scores as well as defect in signaling and energy metabolism in fluorosis patients.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Indian Council of Medical Research		erythrocytes homogenate with ATP [18]. • Total ATPase: assayed using UV-vis spectrophotometer at 660 nm.		
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.

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?	++	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	Were all measured outcomes reported?	++	Outcomes mentioned in the methods section were

Risk of bias assessment			
reporting			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.

Bashash 2017 [\[79\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study Study design: Prospective cohort study	Exposures: <u>Fluoride levels in</u> <ul style="list-style-type: none"> Maternal urinary samples during gestation (proxy measure of prenatal exposure to fluoride) Child urinary samples 	Outcomes: Neurocognitive function in children at 4 years of age, and 6 to 12 years of age Method of outcome	Statistical analysis: <ul style="list-style-type: none"> Linear regression models were used Models assessing maternal urinary fluoride levels as exposure were adjusted for child 	<ul style="list-style-type: none"> Higher prenatal exposure to fluoride (as indicated by average creatinine-adjusted maternal urinary fluoride concentrations during pregnancy) was

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: Mexico</p> <p>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</p> <p>Sampling time frame: <u>Cohort 2A:</u></p>	<p>at 6 to 12 years of age (proxy measure of postnatal exposure to fluoride)</p> <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • 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 	<p>ascertainment:</p> <p><u>Standardized version of McCarthy Scales of Children’s Abilities (MSCA)</u></p> <ul style="list-style-type: none"> • 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 	<p>characteristics (gestational age, birth weight, sex, parity, age at outcome assessment) and maternal characteristics (smoking history, marital status, delivery age, IQ, education, and cohort)</p> <ul style="list-style-type: none"> • Models assessing child urinary fluoride levels were adjusted for the main covariates of interest <p>Results: Change (95% CI) in</p>	<p>associated with lower GCI scores in children at approximately 4y old, and with lower Full-Scale IQ scores at 6–12 y old.</p> <ul style="list-style-type: none"> • 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • May 1997 – July 1999 <p><u>Cohort 3</u></p> <ul style="list-style-type: none"> • 2001 to 2003 <p>Sample size (N): 299 mother-child pairs</p> <p>Sex:</p> <p><u>GCI analysis: Girls</u></p> <ul style="list-style-type: none"> • N (%) = 160 (56) <p><u>IQ analysis: Girls</u></p> <ul style="list-style-type: none"> • N (%) = 116 (55) <p>Exclusions:</p> <ul style="list-style-type: none"> • No gestational urine 	<p>urinary samples were adjusted for specific gravity</p> <p>Exposure levels:</p> <p>Water fluoride levels in Mexico City:</p> <ul style="list-style-type: none"> ○ 0.15 - 1:38 mg/L (Juárez-López <i>et al.</i> 2007; Martínez-Mier <i>et al.</i> 2005). <p>Maternal urinary fluoride (Mean ±SD)</p> <ul style="list-style-type: none"> ○ 0.88 mg/L ±0.34 <p>Child urinary fluoride (Mean ±SD)</p>	<p><u>Other Details</u></p> <ul style="list-style-type: none"> • Experienced developmental psychologist trained and oversaw the administration of tests by three other psychologists • Psychologist conducting the assessment was blinded to the child's exposure level 	<p>outcome per 0.5 mg/L increase in maternal urinary fluoride levels adjusted for creatinine</p> <ul style="list-style-type: none"> • <u>GCI</u> $\beta = -3.15$ (-5.42, -0.87) $p = 0.01$ • <u>IQ</u> $\beta = -2.50$ (-4.12, -0.59) $p = 0.01$ <p>Change (95% CI) in outcome per 0.5 mg/L increase in child urinary fluoride levels adjusted for specific gravity</p>	<p>association between contemporaneous children's urinary fluoride (CUFsg) and IQ either unadjusted or adjusting for MUFcr</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>sample available (Cohort 1 and 2B)</p> <ul style="list-style-type: none"> • > 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, 	<p><i>0.84 mg/L ± 0.40</i></p>		<ul style="list-style-type: none"> • <u>IQ – Without adjustment of maternal urinary fluoride levels</u> $\beta = - 0.89 (-2.63, 0.85)$ • <u>IQ – With adjustment of maternal urinary fluoride levels</u> $\beta = - 0.77 (-2.53, 0.99)$ 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>circulatory disease, and seizures during gestation</p> <ul style="list-style-type: none"> • No neurocognitive function measurement in the child <p>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</p> <p>Author declaration of interest: No competing</p>				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
financial interests				

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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

Risk of bias assessment			
			3 - Intervention; Cohort 3 - Placebo; Cohort 2A).
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+	<p>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).</p> <p>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).</p>
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;

Risk of bias assessment			
			<p>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.</p> <p>In the comparisons of participants in relation to missing data ..., the proportion of females was 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.</p> <p>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).</p>
Detection	Can we be confident in the exposure	+	Fluoride levels were measured in maternal and child

Risk of bias assessment				
	characterization?			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 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	++ Participants were recruited at 14 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

Risk of bias assessment			
			<p>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.</p> <p>assessment was blinded to the child's exposure level. Regression models were adjusted for the age at outcome assessment.</p>
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.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Abstract</p> <p>Study design: NR</p> <p>Country: India</p> <p>Participants: Population exposed to fluoride</p> <p>Sample size (N): 100</p> <p>Sex: Men (100%)</p>	<p>Exposure:</p> <ul style="list-style-type: none"> • Fluoride <p>Method of exposure assessment: NR</p> <p>Exposure level: NR</p>	<p>Outcomes:</p> <ul style="list-style-type: none"> • Semen morphological parameters • Hypothalamic-testicular axis hormones (LH, FSH, prolactin, testosterone) • Oxidative stress markers <p>Method of outcome ascertainment: NR</p>	<p>Statistical analysis: NR</p> <p>Results:</p> <ul style="list-style-type: none"> • “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, 	<ul style="list-style-type: none"> • “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)

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Exclusions: NR</p> <p>Source of funding/ support: NR</p> <p>Author declaration of interest: NR</p>			<p>GPx and GSH was observed.” (p. S236)</p> <ul style="list-style-type: none"> • “Sperm count, motility and viability was delineated in exposed population.” (p. S236) 	

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

Risk of bias assessment			
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
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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference Type: Abstract	Exposure: <ul style="list-style-type: none"> • Fluoridated water 	Outcomes: <ul style="list-style-type: none"> • Suicide rates 	Statistical analysis: <ul style="list-style-type: none"> • Correlation coefficients 	<ul style="list-style-type: none"> • 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 design: NR	Method of exposure assessment:	Method of outcome ascertainment:	Results	
Country: US	<ul style="list-style-type: none"> • State data from the CDC 	<ul style="list-style-type: none"> • NR 	<ul style="list-style-type: none"> • Relationship between fluoridated water and suicide rates: 	
Participants: NR	Exposure levels: NR		<u>Year 2010</u> r= -0.386; p= 0.05	
Sampling time frame: 2010, 2012, and 2014			<u>Year 2012</u> r= -0.324; p= 0.020	
Sample size (N): NR			<u>Year 2014</u> r= -0.342; p= 0.014	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sex: NR</p> <p>Age: NR</p> <p>Exclusions: NR</p> <p>Source of funding/ support: USTAR</p> <p>Author declaration of interest: NR</p>				

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
Selection	Was administered dose or exposure level	N/A	Not applicable

Risk of bias assessment			
	adequately randomized?		
	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
	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

Risk of bias assessment			
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 [\[82\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in ground water</u>	Outcome(s): Dental fluorosis	Statistical analysis: <ul style="list-style-type: none"> • Chi-square test • Multivariable analysis with generalized estimating equation (GEE) regression model 	“Prevalence of dental fluorosis was considerably high, affecting nearly two-thirds of the students, and mainly in government schools and long-
Study design: Cross-sectional study	Method of exposure assessment: The Orion method	Method of outcome ascertainment: <ul style="list-style-type: none"> • Dental examination using Dean’s fluorosis index 		

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Country: India</p> <p>Participants: High school adolescents (12–17 years) from randomly selected government and private schools in urban and rural areas of Kolar taluka (6 villages). All students who were residents of the area since birth were included in the study.</p> <p>Sampling time frame: February - August 2013</p> <p>Sample size:</p>	<p>(Selective Electrode fluoride estimation apparatus)</p> <p>Exposure level: Mean water fluoride:</p> <ul style="list-style-type: none"> • Holur: 0.85 mg/L. • Other 5 villages: ≥ 1.2 mg/L • All 6 villages: 1.4 ± 0.38 	<ul style="list-style-type: none"> • Community fluorosis index (CFI) 	<p>Results: Karl Pearson correlation coefficient (all 6 villages)</p> <ul style="list-style-type: none"> • Mean fluoride level in water: $1.4 \text{ mg/L} \pm 0.38$ • Community fluorosis index: 2.3 ± 0.37 <p>Multivariable regression analysis (GEE) by drinking water source:</p> <ul style="list-style-type: none"> • Fluorosis present: <ul style="list-style-type: none"> ○ Bore well water: 551 (63.7%) ○ Pipe/tape water: 79 (64.8%) • Total: <ul style="list-style-type: none"> ○ Bore well water: 865 ○ Pipe/tape water: 122 • β estimate (95%CI): 	<p>term residents of the area.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
1,026			<ul style="list-style-type: none"> ○ Bore well water: 0.92(-0.32,2.16), p-value: 0.145 ○ Pipe/tape water: 0 	
<p>Sex (N): Boys: 509 (49.6%)</p> <p>Exclusions: NR</p> <p>Source of funding / support: None</p> <p>Author declaration of interest: • No COI</p>				

Risk of bias assessment

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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 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	++	Yes, exposure was measured in water using the Orion method (Selective Electrode fluoride estimation

Risk of bias assessment			
	characterization?		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 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Reference type: Original study</p> <p>Study design: Cross-sectional study</p> <p>Country: Mexico</p> <p>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</p>	<p>Exposures: <u>Fluoride levels in</u></p> <ul style="list-style-type: none"> • Urine samples • Drinking water samples <p>Method of exposure assessment: <u>Urine Samples</u></p> <ul style="list-style-type: none"> • One spot urine sample used • Ion selective electrode was used to measure fluoride <p><u>Water samples</u></p> <ul style="list-style-type: none"> • Water samples were 	<p>Outcomes: <u>Kidney injury biomarkers</u></p> <ul style="list-style-type: none"> • Kidney injury molecule 1 (KIM-1) • Neutrophil gelatinase-associated lipocalin (NGAL) • Serum creatinine (SCr) • MicroRNAs (miRNAs): miR-21, miR200c, and miR-423 • Estimated glomerular filtration rate (eGFR) • Albumin-creatinine 	<p>Statistical analysis:</p> <ul style="list-style-type: none"> • 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 <p>Results:</p>	<ul style="list-style-type: none"> • The correlation of ... fluoride levels 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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>elementary schools</p> <p>Sampling time frame: June 2014</p> <p>Sample size (N): 83</p> <p>Sex: <u>Boys</u> N (%) = 47 (56.63)</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Were not lifetime residents of the study area • Girls with menarche 	<p>collected on March 2015</p> <ul style="list-style-type: none"> • tap and bottled water samples were acquired from 63 participants • Well water samples were acquired at 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 <p>Exposure level: Tap water fluoride,</p>	<p>ratio (ACR)</p> <p>Method of outcome ascertainment:</p> <p><u>KIM-1 and NGAL</u></p> <ul style="list-style-type: none"> • Micro-bead assays • Measured in urine samples <p><u>Urinary albumin, urinary creatinine, and SCr</u></p> <ul style="list-style-type: none"> • Daytona auto-analyzer <p><u>miRNAs</u></p> <ul style="list-style-type: none"> • RNA isolation, reverse transcription, pre-amplification, qPCR, and quantification 	<p>Correlation between urinary levels of fluoride (ppm) and kidney injury biomarkers:</p> <ul style="list-style-type: none"> • <u>KIM-1 (pg/mL)</u> 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> 	<p>association between urine... fluoride... and the kidney injury biomarkers did not show any statistically significant differences (data not shown).</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Has congenital kidney disease or urinary tract infections • Nonsteroidal anti-inflammatory drugs or antibiotics use <p>Source of funding/ support:</p> <ul style="list-style-type: none"> • National Council on Science and Technology • Fundacion Mexico en Harvard • A. C., NIH/NIEHS • Harvard-NIEHS Centre for Environmental Health • HSPH-NIEHS 	<p>mean (range)</p> <ul style="list-style-type: none"> ○ 2.47 ppm (2.08 - 2.94) <p>Urinary fluoride, mean (range)</p> <p>2.18 ppm (0.34 - 8.60)</p>	<ul style="list-style-type: none"> • Measured in urine samples 	<p>r = 0.08; p = 0.45</p> <p>Regression analysis</p> <ul style="list-style-type: none"> • No statistically significant differences reported between fluoride levels in urine and outcome biomarkers 	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Author declaration of interest: None</p>				

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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

Risk of bias assessment			
			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
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

Risk of bias assessment			
			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.
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 [\[84\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u>	Outcome(s): Dental fluorosis	Statistical analysis: • Prevalence of dental fluorosis	“The prevalence of fluorosis was high, though the severity

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional</p> <p>Country: Brazil</p> <p>Participants: 11 to 14-year-old school children with fully erupted permanent teeth, signed informed consent, and completed socio-demographic questionnaire.</p> <p>Sampling time frame: 2011</p>	<ul style="list-style-type: none"> • Water <p>Method of exposure assessment:</p> <p>NR</p> <p>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</p>	<p>Method of outcome ascertainment:</p> <p>Assessment conducted by dental surgeons using the Thylstrup-Fejerskov (TF) Index</p>	<ul style="list-style-type: none"> • Descriptive data analysis <p>Results:</p> <ul style="list-style-type: none"> • The prevalence of fluorosis was 77.9% (n = 445). • 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: <ul style="list-style-type: none"> ○ 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 	<p>was low in individuals exposed to fluoridation since birth.”</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Sample size: 571 (out of 596)</p> <p>Sex (N): NR</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • 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 <p>Source of funding / support:</p>			<ul style="list-style-type: none"> ○ 76% used infant toothpaste, and 64% reported swallowing this toothpaste 	

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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	N/A Not applicable

Risk of bias assessment		
	study groups?	
	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

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	

Heck 2016 [\[85\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Dissertation Study design: Cross-sectional study Country:	Exposures: • Fluoridated water Method of exposure assessment: • Data from the 1992 Fluoridation Census and the 1990 Census were combined to	Outcomes: • Trouble working • Retardation • General health Method of outcome ascertainment: <u>Trouble working in</u>	Statistical analysis: • Linear regression models used • Models adjusted for race, sex, urban status, and income. Results: Change (standard	No evidence of an effect of water fluoridation on general health, trouble working for children or adults, retardation in children.

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>U.S.</p> <p>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)</p> <p>Sampling time frame: NR</p> <p>Sample size (N):</p>	<p>acquire the proportion of individuals with optimally fluoridated water in a county</p> <ul style="list-style-type: none"> • The same fluoridation exposure is given to all individuals in the same county <p>Exposure levels: NR</p>	<p><u>children and adults:</u></p> <ul style="list-style-type: none"> • Self-reported • Difficulty conducting specific activities (housework, gardening, exercise, or play) • Categories: No difficulty, some difficulty, moderate difficulty, and could not do <p><u>Retardation in children</u></p> <ul style="list-style-type: none"> • Self-reported • Physician diagnosed mental retardation <p><u>General Health in children and adults</u></p>	<p>error; SE) in outcome from the effect of residential optimal water fluoridation among children</p> <ul style="list-style-type: none"> • <u>Trouble working (N = 2,583)</u> $\beta = 0.039 (0.039)$ • <u>Retardation (N = 4,796)</u> $\beta = 0.001 (0.002)$ • <u>General Health (N = 4,618)</u> $\beta = -0.159 (0.165)$ <p>Change (SE) in outcome from the effect of optimal water</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> • Counties: 35 • Populations: > 500,000 <p>Sex: NR</p> <p>Exclusions: NR</p> <p>Source of funding/ support: NR</p> <p>Author declaration of interest: NR</p>		<ul style="list-style-type: none"> • General health of participant as decided by physician • Categories: Excellent, very good, good, fair, and poor 	fluoridation among adults <ul style="list-style-type: none"> • <u>Trouble working (N = 7,100)</u> $\beta = 0.041 (0.043)$ • <u>General health (N = 7,088)</u> $\beta = -0.028 (0.143)$ 	

Risk of bias assessment			
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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
Attrition	Were outcome data complete without	-	Not reported.

Risk of bias assessment						
	attrition or exclusion from analysis?					
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.	++
Selective	Were all measured outcomes reported?	++	Yes, results were reported for general health, trouble			

Risk of bias assessment			
reporting			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 [\[36\]](#)

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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>ecological study</p> <p>Country: India</p> <p>Participants: Children (6 to 18 years of age) from Simlapal Block in Bankura District</p> <p>Sampling time frame: NR</p> <p>Sample size (N): 149</p> <p>Sex: <u>Boys</u></p>	<p>Method of exposure assessment:</p> <p><u>Water samples</u></p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> Fluoride level Water intake/day 	<p>Method of outcome ascertainment:</p> <p><u>BMI</u></p> <ul style="list-style-type: none"> • Information needed for calculations were acquired from 8 primary schools <p><u>IQ</u></p> <ul style="list-style-type: none"> • 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 	<p>urinary fluoride and exposure dose</p> <p>$r = 0.513$; $p = <0.01$</p> <ul style="list-style-type: none"> • Correlation between urinary fluoride and BMI <p>$r = 0.022$; p not <0.01</p> <ul style="list-style-type: none"> • Correlation between urinary fluoride and IQ <p>$r = -0.751$; $p = <0.01$</p> <ul style="list-style-type: none"> • Correlation between exposure dose and BMI <p>$r = -0.083$; p not <0.01</p> <ul style="list-style-type: none"> • Correlation between exposure dose and IQ <p>$r = -0.343$; $p = <0.01$</p> <ul style="list-style-type: none"> • Relationship between 	<p>with IQ ($r = -0.343$, $P < 0.01$), and a non-significant correlation with BMI ($r = 0.083$).</p> <ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • N = 66 <p>Exclusions: NR</p> <p>Source of funding/support: NR</p> <p>Author declaration of interest: NR</p>	<p>Body weight</p> <p><u>Urine samples</u></p> <ul style="list-style-type: none"> • Measured using ion-selective electrode <p>Exposure levels:</p> <ul style="list-style-type: none"> • Mean (SD) levels of fluoride in water samples <p>2.11 mg/L (1.64)</p> <ul style="list-style-type: none"> • Levels of fluoride in urine samples <p>Min = 0.45 mg/L</p> <p>Max = 17.00 mg/L</p>	<p>Retarded/low: ≤ 69</p> <p>Borderline: 79 - 79</p> <p>Below average: 80 – 89</p> <p>Average: 90 – 109</p> <p>Above average: 110 – 119</p> <p>Excellent: 120 – 129</p> <p>Outstanding: ≥ 130</p>	<p>exposure dose and BMI among boys age 6-8 years</p> <p>BMI = 13.9 - 2.7 ED</p> <p>r = 0.073</p> <p>p = 0.832</p> <ul style="list-style-type: none"> • Relationship between exposure dose and BMI among girls age 6-8 years <p>BMI = 13.3 + 29.3 ED</p> <p>r = 0.092</p> <p>p = 0.716</p> <ul style="list-style-type: none"> • Relationship between exposure dose and BMI among boys age 8-10 year <p>BMI = 15.3 – 12.7 ED</p>	

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
			<p>$r = 0.124$ $p = 0.451$</p> <ul style="list-style-type: none"> • Relationship between exposure dose and BMI among girls age 8-10 years <p>BMI = 14.1 – 5.69 ED</p> <p>$r = 0.144$ $p = 0.362$</p> <ul style="list-style-type: none"> • Relationship between exposure dose and BMI among boys age >10 years <p>BMI = 17.3 – 20.1 ED</p> <p>$r = 0.217$ $p = 0.371$</p> <ul style="list-style-type: none"> • Relationship between exposure dose and 	

Study Characteristics

Study	Exposure	Outcome	Analysis & Results	Conclusions
			BMI among girls age >10 years BMI = 14.3 + 3.63 ED r = 0.133 p = 0.575	

Risk of bias assessment

<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>	
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

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?	++	No mention of excluding participants or missing data.		
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	++	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

Risk of bias assessment				
			blinding status.	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.	
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 [\[87\]](#)

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
Reference type: Original study	Exposures: <u>Fluoride levels in</u>	Outcome(s): • Dental fluorosis	Statistical analysis: • Logistic regression was used to assess the	• "Fluorosis indices, if used alone, could result in

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional study</p> <p>Country: Iran</p> <p>Participants: Children (9 years of age) randomly selected from locations with high, optimal, and low fluoride drinking water levels in Fars</p> <p>Sampling time frame: NR</p> <p>Sample size:</p>	<ul style="list-style-type: none"> • Water <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Acquired from the town's primary health care trust <p>Exposure level:</p> <p>Fluoride levels by town and category of exposure:</p> <p><u>Gerash (high fluoride)</u></p> <ul style="list-style-type: none"> • 2.12 – 2.85 ppm <p><u>Sepidan (low fluoride)</u></p> <ul style="list-style-type: none"> • 0.24 – 0.29 ppm <p><u>Shiraz (optimal fluoride)</u></p> <ul style="list-style-type: none"> • 0.62 – 1.22 ppm 	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • Dentists assessed photos using the Dean's Index and Thylstrup and Fejerskov (TF) Index 	<p>association between fluoride drinking water levels and fluorosis</p> <p>Results:</p> <p>Percentage of genuine fluorosis by exposure categories</p> <ul style="list-style-type: none"> • High Water Fluoride: 47.7% • Optimal Water Fluoride: 20.6% • Low Water Fluoride: 3.3% • p-value: <0.001 <p>Odds (95% CI) of genuine fluorosis with optimal compared to high fluoride levels:</p>	<p>misdiagnosis of dental fluorosis and misguide health policymakers in their decision about public health measure related to use of fluoride."</p> <ul style="list-style-type: none"> • "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
376			<ul style="list-style-type: none"> • 0.292 (0.168 – 0.506) 	
Sex (N): Boys: 196 (53%)			Odds (95% CI) of genuine fluorosis with low compared to high fluoride levels:	
Exclusions: <ul style="list-style-type: none"> • 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 			<ul style="list-style-type: none"> • 0.037 (0.011 – 0.127) 	
Source of funding / support:				

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<ul style="list-style-type: none"> Vice-Chancellery for Research of Shiraz University of Medical Science <p>Author declaration of interest:</p> <p>No COI</p>				

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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	+ Yes, participants were selected using the same criteria. However, the sampling timeframe was not reported

Risk of bias assessment		
	appropriate comparison groups?	
Confounding	Did the study design or analysis account for important confounding and modifying variables?	+ Study accounted only for 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?	++ 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

Risk of bias assessment				
				dentists of each group agreed. 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 appropriate and researchers adhered to the study protocol)?	++		None identified

Xiang 2016 [\[88\]](#)

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

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p>Study design: Cross-sectional study</p> <p>Country: China</p> <p>Participants: Children (8 – 14 years of age) from Wamiao and Xinhuai</p> <p>Sampling time frame: • 2002: before defluoridation • 2013: 10 years after defluoridation</p> <p>Sample size (N):</p>	<p>sources</p> <p>Method of exposure assessment:</p> <ul style="list-style-type: none"> • Fluoride ion selective electrode <p>Exposure level:</p> <p>Mean fluoride level in tap water (SD) in 2013</p> <p><u>Wamiao</u></p> <ul style="list-style-type: none"> • 0.91 mg/L (0.02) <p><u>Xinhuai</u></p> <p>0.89 mg/L (0.03)</p>	<p>Method of outcome ascertainment:</p> <ul style="list-style-type: none"> • 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” <p>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</p>	<p>fluorosis were calculated</p> <p>Results:</p> <ul style="list-style-type: none"> • “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 $r=0.999$, $y=99.552/(1+40.049x e^{-3.464x})$, 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 	<p>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)</p>

Study Characteristics				
Study	Exposure	Outcome	Analysis & Results	Conclusions
<p><u>2002:</u></p> <ul style="list-style-type: none"> • Wamiao = 236 • Xinhuai = 290 <p><u>2013:</u></p> <ul style="list-style-type: none"> • Wamiao = 68 • Xinhuai = 65 <p>Sex (N):</p> <p><u>Wamiao in 2002</u></p> <p>Men: 130 (55.1%)</p> <p><u>Xinhuai in 2002</u></p> <p>Men: 159 (54.8%)</p> <p>Exclusions:</p> <p><u>2013 participants</u></p> <p>Absent from village for</p>		<p>fluorosis (grade 3) and all “severe” dental fluorosis (grade 4) as diagnosed by Dean’s criteria” (p. 25)</p>	<p>decreased with the decreased drinking water fluoride in Wamiao in 2013 after defluoridation compared with the results in 2002.” (p. 23)</p>	

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

Risk of bias assessment		
<i>Bias domain</i>	<i>Criterion</i>	<i>Response</i>
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 (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 dental fluorosis" (WS/T208-2001). Lack of blinding of outcome assessors would not appreciably 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

Section 4. Excluded animal studies (with reasons for exclusion)

Level	Bibliography	Reason for Exclusion
L1	<i>Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports. 2019. 10:23</i>	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. <i>Bioconjug Chem. 2010. 21:360-71</i>	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. <i>ACS Appl Mater Interfaces. 2016. 8:4467-76</i>	One or more exclusion criteria
L1	Sinha, S.,Vorse, K. S.,Kariya, P. B.,Mallikarjuna, R.. 'Pitted' to 'pleasing' in 20 min. <i>BMJ Case Reports. 2015. #volume#:#pages#</i>	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. <i>Journal of Labelled Compounds and Radiopharmaceuticals. 2019. 62 (Supplement 1):S166-S168</i>	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. <i>Journal of Immunology. Conference: 101st Annual Meeting of the American Association of Immunologist, IMMUNOLOGY. 2014. 192:#pages#</i>	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
L1	Chopra, A.. (99m)Tc-glutamate peptide 3-aminoethyl estradiol. <i>Molecular Imaging and Contrast Agent Database (MICAD)</i> . 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. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 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. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2015. 1):S282	One or more exclusion criteria
L1	Sviripa, V. M.,Zhang, W.,Balija, 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. <i>J Med Chem</i> . 2014. 57:6083-91	One or more exclusion criteria
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. <i>Bioorganic & Medicinal Chemistry Letters</i> . 2013. 23:3920-6	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
L1	Connett, P.. 3rd Citizens Conference of the Fluoride Action Network. <i>Fluoride</i> . 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. <i>Front Physiol</i> . 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. <i>Inorg Chem</i> . 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.. ⁶⁸ Ga-PSMA-11: An one-year performance experience on a single vial kit-type preparation of a potent PET radiodiagnostic agent for prostate cancer imaging. <i>Molecular Imaging and Biology</i> . 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. <i>Acc Chem Res</i> . 2016. 49:1333-43	One or more exclusion criteria
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. <i>Osteoarthritis and Cartilage</i> . 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.. [¹⁸ F]DPA-716 as a candidate for imaging the TSPO 18 kDa with PET: Radiosynthesis and comparative	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	evaluation ([¹¹ C]DPA-713 / [¹⁸ F]DPA-714) in a rat model of neuroinflammation. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2011. 1):S275	
L1	Riondato, M.,Pastorino, S.,Giovannini, E.,Ferrando, O.,Lazzeri, P.,Duce, V.,Ciarmiello, A.. [¹⁸ F]FET production with a modified gallium-68 automated synthesizer in a Radiopharmacy without cyclotron facility. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2019. 46 (1 Supplement 1):S723	One or more exclusion criteria
L1	Xiong, L.,Shen, B.,Gambhir, S. S.,Chin, F. T.,Rao, J.. [¹⁸ F]YF ₃ nanoprobe: Novel 18F-labeled imaging agents for tumor targeting. <i>Molecular Imaging and Biology</i> . 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 disease. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2011. 1):S455	One or more exclusion criteria
L1	Palczewska-Komsa, M.. [Comparison of fluoride concentrations in human, dog, fox and raccoon dog bones from northwestern Poland]. <i>Pomeranian J Life Sci</i> . 2015. 61:319-28	One or more exclusion criteria
L1	Machoy-Mokrzyńska, A.,Machoy, Z.. [Current trends in fluorine research]. <i>Ann Acad Med Stetin</i> . 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	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	consuming water with different fluoride concentrations in Maiquetia, Vargas State, Venezuela]. <i>Invest Clin.</i> 2007. 48:5-19	
L1	Golubkina, N. A.,Burtseva, T. I.,Gatsenko, Alu. [Drinking water quality indices in the Orenburg Region]. <i>Gig Sanit.</i> 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]. <i>Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology.</i> 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 health disparities among urban children in Burkina Faso]. <i>Rev Epidemiol Sante Publique.</i> 2011. 59:385-92	One or more exclusion criteria
L1	Smoliar, N. I.,Bezvushko, E. V.,Chukhrai, N. L.,Dzhaser, A. Kh. [Incidence of malocclusion in children living in areas with high fluoride content in water]. [Russian]. <i>Stomatologija.</i> 2014. 93:52-54	One or more exclusion criteria
L1	Skudarnov, S. E.,Kurkatov, S. V.. [Incidence of non-communicable diseases and health risks due to potable water quality]. [Russian]. <i>Gigiena i sanitariia.</i> 2011. #volume#:30-32	One or more exclusion criteria
L1	de Carvalho, R. B.,Medeiros, U. V.,dos Santos, K. T.,Pacheco Filho, A. C.. [Influence of different concentrations of fluoride in the water on epidemiologic	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	indicators of oral health/disease]. <i>Cien Saude Colet.</i> 2011. 16:3509-18	
L1	Chen, L. W.,Gu, S.,Jia, X. Y.. [Occluding effects of desensitizer containing NovaMin combined with fluor protector on dentinal tubules:an in vitro study]. <i>Shanghai Kou Qiang Yi Xue.</i> 2015. 24:535-40	One or more exclusion criteria
L1	Wang, X. L.,Ming, J.,Qiu, B.,Liao, Y. F.,Liao, Y. D.,Wei, S. F.,Tu, C. L.,Pan, X. L.. [Relationship between fluoride exposure, orthopedic injuries and bone formation markers in patients with coal-burning fluorosis]. <i>Ying Yong Sheng Tai Xue Bao.</i> 2019. 30:43-48	One or more exclusion criteria
L1	Carvalho, R. W.,Valois, R. B.,Santos, C. N.,Marcellini, P. S.,Bonjardim, L. R.,Oliveira, C. C.,Barretto, S. R.,Goncalves, S. R.. [Study of the prevalence of dental fluorosis in Aracaju]. [Portuguese]. <i>Ciencia & saude coletiva.</i> 2010. 15 Suppl 1:1875-1880	One or more exclusion criteria
L1	Drobnik, M.,Latour, T.,Sziwa, D.. [The assessment of health exposure resulted from barium, boron, and fluoride intake from therapeutic waters available for resident people in water abstraction points of health resorts]. [Polish]. <i>Roczniki Panstwowego Zakladu Higieny.</i> 2010. 61:373-378	One or more exclusion criteria
L1	Romero, V.,Norris, F. J.,Rios, J. A.,Cortes, I.,Gonzalez, A.,Gaete, L.,Tchernitchin, A. N.. [The impact of tap water fluoridation on human health]. <i>Revista Medica de Chile.</i> 2017. 145:240-249	One or more exclusion criteria
L1	Jaudenes Marrero, J. R.,Hardisson de la Torre, A.,Gutierrez Fernandez, A. J.,Rubio Armendariz, C.,Revert Girones, C.. [Toxic Risk Assessment of Fluoride Presence	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	in Bottled Water Consumption in the Canary Islands]. <i>Nutricion Hospitalaria</i> . 2015. 32:2261-8	
L1	Janka, Z.. [Tracing trace elements in mental functions]. <i>Ideggyogy Sz.</i> 2019. 72:367-379	One or more exclusion criteria
L1	Orsini, G.,Procaccini, M.,Manzoli, L.,Sparabombe, S.,Tiriduzzi, P.,Bambini, F.,Putignano, A.. A 3-day randomized clinical trial to investigate the desensitizing properties of three dentifrices. <i>J Periodontol</i> . 2013. 84:e65-73	One or more exclusion criteria
L1	Choubisa, S. L.. A brief and critical review on hydrofluorosis in diverse species of domestic animals in India. <i>Environ Geochem Health</i> . 2018. 40:99-114	One or more exclusion criteria
L1	Chen, S.,Song, L.,Xie, X.,Han, X.,Cheng, B.. A case of abdominal mesenteric Castleman's disease with left renal cell carcinoma and stomach leiomyoma. <i>Hellenic Journal of Nuclear Medicine</i> . 2016. 19:285-288	One or more exclusion criteria
L1	Mosaferi, M.,Feizi, M. A. H.,Dastgiri, S.,Kusha, A.,Mehdipour, M.. A case study of dental fluorosis prevalence in rural communities in Northwest Iran. <i>Fluoride</i> . 2012. 45 (3 PART 1):185-186	One or more exclusion criteria
L1	Malar, S.,Karuppanan, S.,Krishnaveni, M.,Venkateswaran, S.. A case study on dental fluorosis in Uthangarai Taluk, Krishnagiri District, Tamil Nadu, India. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences</i> . 2011. 13:47-49	One or more exclusion criteria
L1	Sharma, N.,Roy, S.,Kakar, A.,Greenspan, D. C.,Scott, R.. A clinical study comparing oral formulations containing 7.5% calcium sodium phosphosilicate (NovaMin), 5% potassium	One or more exclusion criteria

Level	Bibliography	Reason for Exclusion
	nitrate, and 0.4% stannous fluoride for the management of dentin hypersensitivity. <i>J Clin Dent.</i> 2010. 21:88-92	
L1	Shruthi, M. N.,Anil, N. S.. A comparative study of dental fluorosis and non-skeletal manifestations of fluorosis in areas with different water fluoride concentrations in rural Kolar. <i>Journal of Family Medicine & Primary Care.</i> 2018. 7:1222-1228	One or more exclusion criteria
L1	Shruthi, M. N.,Santhuram, A. N.,Arun, H. S.,Kishore Kumar, B. N.. A comparative study of skeletal fluorosis among adults in two study areas of Bangarpet taluk, Kolar. <i>Indian J Public Health.</i> 2016. 60:203-9	One or more exclusion criteria
L1	Poureslami, H. R.,Horri, A.,Garrusi, B.. A comparative study of the IQ of children age 7-9 in a high and a low fluoride water city in Iran. <i>Fluoride.</i> 2011. 44:163-167	One or more exclusion criteria
L1	Yu, J.,Zhou, J.,Long, A.,He, X.,Deng, X.,Chen, Y.. A comparative study of water quality and human health risk assessment in longevity area and adjacent non-longevity area. <i>International Journal of Environmental Research and Public Health.</i> 2019. 16 (19) (no pagination):#pages#	One or more exclusion criteria
L1	Macey, R.,Tickle, M.,MacKay, L.,McGrady, M.,Pretty, I. A.. A comparison of dental fluorosis in adult populations with and without lifetime exposure to water fluoridation. <i>Community Dent Oral Epidemiol.</i> 2018. 46:608-614	One or more exclusion criteria
L1	González-Horta, C.,Ballinas-Casarrubias, L.,Sánchez-Ramírez, B.,Ishida, M. C.,Barrera-Hernández, A.,Gutiérrez-Torres, D.,Zacarias, O. L.,Saunders, R. J.,Drobná, Z.,Mendez, M. A.,García-Vargas, G.,Loomis, D.,Stýblo, M.,Del Razo, L. M.. A concurrent exposure to arsenic and	One or more exclusion criteria

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L1	Henry, B. J.,Carlin, J. P.,Hammerschmidt, J. A.,Buck, R. C.,Buxton, L. W.,Fiedler, H.,Seed, J.,Hernandez, O.. A critical review of the application of polymer of low concern and regulatory criteria to fluoropolymers. <i>Integr Environ Assess Manag</i> . 2018. 14:316-334	One or more exclusion criteria
L1	Chen, P.,He, D.,Wei, S.,Pu, G.,La, C.,Jiang, H.,Li, S.,Lu, Q.,Zhao, Y.. A cross-sectional investigation of drinking brick-tea fluorosis of children aged 8 - 12 in Qinghai Province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2014. 33:53-55	One or more exclusion criteria
L1	Sebastian, S. T.,Sunitha, S.. A cross-sectional study to assess the intelligence quotient (IQ) of school going children aged 10-12 years in villages of Mysore district, India with different fluoride levels. <i>J Indian Soc Pedod Prev Dent</i> . 2015. 33:307-11	One or more exclusion criteria
L1	Zhang, B.,Li, M.,Zhou, S.,Dai, X.,Xiong, P.,Zhu, S.. A dental fluorosis trend analysis of children aged 8 to 12 in drinking-water-type endemic fluorosis areas of Hubei Province from 2010 to 2014. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2016. 35:664-667	One or more exclusion criteria
L1	Orsini, G.,Procaccini, M.,Manzoli, L.,Giuliodori, F.,Lorenzini, A.,Putignano, A.. A double-blind randomized-controlled trial comparing the desensitizing efficacy of a	One or more exclusion criteria

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L1	Ke, B.,Chen, W.,Ni, N.,Cheng, Y.,Dai, C.,Dinh, H.,Wang, B.. A fluorescent probe for rapid aqueous fluoride detection and cell imaging. <i>Chem Commun (Camb).</i> 2013. 49:2494-6	One or more exclusion criteria
L1	Kotoky, P.,Tamuli, U.,Borah, G. C.,Baruah, M. K.,Sarmah, B. K.,Paul, A. B.,Bhattacharyya, K. G.. A fluoride zonation map of the Karbianglong District, Assam, India. <i>Fluoride.</i> 2010. 43:157-159	One or more exclusion criteria
L1	Rodnick, M. E.,Brooks, A. F.,Hockley, B. G.,Henderson, B. D.,Scott, P. J. H.. A fully automated one-pot high yielding synthesis of [¹⁸ F]fluoromethylcholine. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2013. 1):S117	One or more exclusion criteria
L1	Fordyce, F. M.,Vrana, K.,Zhovinsky, E.,Povoroznuk, V.,Toth, G.,Hope, B. C.,Iljinsky, U.,Baker, J.. A health risk assessment for fluoride in Central Europe. <i>Environ Geochem Health.</i> 2007. 29:83-102	One or more exclusion criteria
L1	Hongyong, W.,Zou, P.,Xie, M.,Liu, Y.,Wu, J.,Wu, H.. A high yield automated synthesis of ¹⁸ F-FLT On PET-MF- 2V-IT-I module with SPE purification. <i>European Journal of Nuclear Medicine and Molecular Imaging.</i> 2019.	One or more exclusion criteria

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L1	Tanifum, E. A., Devkota, L., Ngwa, C., Badachhape, A. A., Ghaghada, K. B., Romero, J., Pautler, R. G., Annapragada, A. V.. A Hyperfluorinated Hydrophilic Molecule for Aqueous (19)F MRI Contrast Media. <i>Contrast Media Mol Imaging</i> . 2018. 2018:1693513	One or more exclusion criteria
L1	Ghosh, P., Banerjee, P.. A Journey towards Salivary Fluoride Level Detection by Suitable Low Cost Chemosensor: From Molecule to Product. <i>Chem Rec</i> . 2019. 19:2119-2129	One or more exclusion criteria
L1	Khare, P.. A large-scale investigation of the quality of groundwater in six major districts of Central India during the 2010-2011 sampling campaign. <i>Environmental Monitoring and Assessment</i> . 2017. 189 (9) (no pagination):#pages#	One or more exclusion criteria
L1	Chen, L., Wang, W., Su, B., Wen, Y., Li, C., Zhou, Y., Li, M., Shi, X., Du, H., Song, Y., Jiang, L.. A light-responsive release platform by controlling the wetting behavior of hydrophobic surface. <i>ACS Nano</i> . 2014. 8:744-51	One or more exclusion criteria
L1	Shaw, F. E.. A message from the editor. <i>Public Health Reports</i> . 2015. 130:295	One or more exclusion criteria
L1	Gill, H. S., Tinianow, J. N., Ogasawara, A., Flores, J. E., Vanderbilt, A. N., Raab, H., Scheer, J. M., Vandlen, R., Williams, S. P., Marik, J.. A modular platform for the rapid site-specific radiolabeling of proteins with 18F exemplified by quantitative positron emission tomography of human epidermal growth factor receptor 2. <i>J Med Chem</i> . 2009. 52:5816-25	One or more exclusion criteria

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L1	Girardi, P.,Merler, E.. A mortality study on male subjects exposed to polyfluoroalkyl acids with high internal dose of perfluorooctanoic acid. <i>Environmental Research</i> . 2019. Part A. 179 (no pagination):#pages#	One or more exclusion criteria
L1	Qiao, F.,Pan, T.,Clark, J. W., Jr.,Mawlawi, O. R.. A motion-incorporated reconstruction method for gated PET studies. <i>Phys Med Biol</i> . 2006. 51:3769-83	One or more exclusion criteria
L1	Wang, C.,Gao, Y.,Wang, W.,Zhao, L.,Zhang, W.,Han, H.,Shi, Y.,Yu, G.,Sun, D.. A national cross-sectional study on effects of fluoride-safe water supply on the prevalence of fluorosis in China. <i>BMJ Open</i> . 2012. 2:#pages#	One or more exclusion criteria
L1	Maltais, R.,Ayan, D.,Poirier, D.. A new aminosteroid (RM-133) as selective anti-cancer agent: Chemical synthesis and biological activities. <i>Drugs of the Future</i> . 2010. A):256	One or more exclusion criteria
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L1	Inkster, J. A.,Colin, D. J.,Seimbille, Y.. A novel 2-cyanobenzothiazole-based (18)F prosthetic group for conjugation to 1,2-aminothiol-bearing targeting vectors. <i>Org Biomol Chem</i> . 2015. 13:3667-76	One or more exclusion criteria
L1	Meziane, I.,Jerome, D.,Johnny, V.,Danie, S.,Denis, G.,Louisa, B.. A novel [¹⁸ F]AV-45 (Florbetapir) synthesis for a fully automated development on a tracer lab MX ^{FDG} apparatus. <i>Journal of</i>	One or more exclusion criteria

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L1	Kumari, U.,Behera, S. K.,Meikap, B. C.. A novel acid modified alumina adsorbent with enhanced defluoridation property: Kinetics, isotherm study and applicability on industrial wastewater. <i>Journal of Hazardous Materials</i> . 2019. 365:868-882	One or more exclusion criteria
L1	Tirapelli, C.,Panzeri, H.,Soares, R. G.,Peitl, O.,Zanotto, E. D.. A novel bioactive glass-ceramic for treating dentin hypersensitivity. <i>Braz Oral Res</i> . 2010. 24:381-7	One or more exclusion criteria
L1	Laverman, P.,McBride, W. J.,Sharkey, R. M.,Eek, A.,Joosten, L.,Oyen, W. J.,Goldenberg, D. M.,Boerman, O. C.. A novel facile method of labeling octreotide with (18)F-fluorine. <i>J Nucl Med</i> . 2010. 51:454-61	One or more exclusion criteria
L1	He, J.,Matsuura, T.,Chen, J. P.. A novel Zr-based nanoparticle-embedded PSF blend hollow fiber membrane for treatment of arsenate contaminated water: Material development, adsorption and filtration studies, and characterization. <i>Journal of Membrane Science</i> . 2014. 452:433-445	One or more exclusion criteria
L1	Zheng, F.,Zeng, F.,Yu, C.,Hou, X.,Wu, S.. A PEGylated fluorescent turn-on sensor for detecting fluoride ions in totally aqueous media and its imaging in live cells. <i>Chemistry</i> . 2013. 19:936-42	One or more exclusion criteria
L1	Mazur, C. M.,Savic, D.,Pedoia, V.,Venkatachari, A. K.,Seo, Y.,Franc, B. L.,Majumdar, S.. A PET/MR study of cartilage-bone interactions in osteoarthritis using $T_{1\rho}$ dispersion. <i>Molecular Imaging and Biology</i> . 2016. 1):S759-	One or more exclusion criteria

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L1	Kong, X. Y., Hou, L. J., Shao, X. Q., Shuang, S. M., Wang, Y., Dong, C.. A phenolphthalein-based fluorescent probe for the sequential sensing of Al(3+) and F(-) ions in aqueous medium and live cells. <i>Spectrochim Acta A Mol Biomol Spectrosc.</i> 2019. 208:131-139	One or more exclusion criteria
L1	Schafer, D., Zlatopolskiy, B. D., Ermert, J., Neumaier, B.. A practical two-step synthesis of 5-[¹⁸ F]fluoro-L-tryptophan (5-[¹⁸ F]FTrp) via alcohol-enhanced Cu-mediated radiofluorination. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2017. 60 (Supplement 1):S105	One or more exclusion criteria
L1	Lie, M., Thorstensen, K.. A precise, sensitive and stable LC-MSMS method for detection of picomolar levels of serum aldosterone. <i>Scand J Clin Lab Invest.</i> 2018. 78:379-385	One or more exclusion criteria
L1	Dickson, R. C.. A reader and author respond to "The top ten unfounded health scares of the year". <i>MedGenMed Medscape General Medicine.</i> 2008. 10 (4) (no pagination):#pages#	One or more exclusion criteria
L1	Cárdenas-Rodríguez, J., Howison, C. M., Matsunaga, T. O., Pagel, M. D.. A reference agent model for DCE MRI can be used to quantify the relative vascular permeability of two MRI contrast agents. <i>Magn Reson Imaging.</i> 2013. 31:900-10	One or more exclusion criteria
L1	Rasool, A., Farooqi, A., Xiao, T., Ali, W., Noor, S., Abiola, O., Ali, S., Nasim, W.. A review of global outlook on fluoride contamination in groundwater with prominence on the Pakistan current situation. <i>Environ Geochem Health.</i> 2018.	One or more exclusion criteria

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L1	Chang, W.,Wang, L.,Zhang, Y.,Wang, M.,Wang, Y.,Li, P.. A review of sources, multimedia distribution and health risks of novel fluorinated alternatives. <i>Ecotoxicology and Environmental Safety</i> . 2019. 182 (no pagination):#pages#	One or more exclusion criteria
L1	Chang, C. W.,Chou, T. K.,Liu, R. S.,Wang, S. J.,Lin, W. J.,Chen, C. H.,Wang, H. E.. A robotic synthesis of [18F]fluoromisonidazole ([18F]FMISO). <i>Appl Radiat Isot</i> . 2007. 65:682-6	One or more exclusion criteria
L1	Tago, T.,Toyohara, J.,Fujimaki, R.,Hirano, K.,Iwai, K.,Ishibashi, K.,Tanaka, H.. A simple SPE purification method for ¹⁸ F-radiolabeling: Proof-of-concept study in stilbene amyloid-beta ligands with a neopentyl labeling group. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2019. 62 (Supplement 1):S163-S164	One or more exclusion criteria
L1	Wright, J. A.,Cronin, A.,Okotto-Okotto, J.,Yang, H.,Pedley, S.,Gundry, S. W.. A spatial analysis of pit latrine density and groundwater source contamination. <i>Environ Monit Assess</i> . 2013. 185:4261-72	One or more exclusion criteria
L1	Zhang, R.,Niu, Y.,Du, H.,Cao, X.,Shi, D.,Hao, Q.,Zhou, Y.. A stable and sensitive testing system for potential carcinogens based on DNA damage-induced gene	One or more exclusion criteria

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L1	You, H., Fu, S., Qin, X., Yu, Y., Yang, B., Zhang, G., Sun, X., Feng, Y., Chen, Y., Wu, J.. A study of the synergistic effect of folate-decorated polymeric micelles incorporating Hydroxycamptothecin with radiotherapy on xenografted human cervical carcinoma. <i>Colloids Surf B Biointerfaces</i> . 2016. 140:150-160	One or more exclusion criteria
L1	Boyle, P., Koechlin, A., Autier, P.. A systematic review with meta-analysis of fluoridated mouthwash use for the prevention of dental caries. <i>Oral Diseases</i> . 2014. 20:27-34	One or more exclusion criteria
L1	Hoover, A. J., Lazari, M., Ren, H., Narayanam, M. K., Murphy, J. M., van Dam, R. M., Hooker, J. M., Ritter, T.. A Transmetalation Reaction Enables the Synthesis of $[(^{18}F)5\text{-Fluorouracil}]$ from $[(^{18}F)\text{Fluoride}]$ for Human PET Imaging. <i>Organometallics</i> . 2016. 35:1008-1014	One or more exclusion criteria
L1	Thompson, S., Onega, M., Ashworth, S., Fleming, I. N., Passchier, J., O'Hagan, D.. A two-step fluorinase enzyme mediated (^{18}F) labelling of an RGD peptide for positron emission tomography. <i>Chem Commun (Camb)</i> . 2015. 51:13542-5	One or more exclusion criteria
L1	Buyukkaplan, U. S., Aksoy, A., Komerik, N., Yilmaz, H.	One or more exclusion

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L1	Li, Y.,Wang, S.,Prete, D.,Xue, S.,Nan, Z.,Zang, F.,Zhang, Q.. Accumulation and interaction of fluoride and cadmium in the soil-wheat plant system from the wastewater irrigated soil of an oasis region in northwest China. <i>Sci Total Environ</i> . 2017. 595:344-351	One or more exclusion criteria
L1	Li, Y.,Wang, S.,Nan, Z.,Zang, F.,Sun, H.,Zhang, Q.,Huang, W.,Bao, L.. Accumulation, fractionation and health risk assessment of fluoride and heavy metals in soil-crop systems in northwest China. <i>Sci Total Environ</i> . 2019. 663:307-314	One or more exclusion criteria
L1	Khan, N. B.,Chohan, A. N.. Accuracy of bottled drinking water label content. <i>Environmental Monitoring and Assessment</i> . 2010. 166:169-176	One or more exclusion criteria
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. <i>British Journal of Dermatology</i> . 2010. 1):87-88	One or more exclusion criteria
L1	Panziera, W.,Schwertz, C. I.,da Silva, F. S.,Taunde, P. A.,Pavarini, S. P.,Driemeier, D.. Acute sodium fluorosilicate poisoning in cattle. [Portuguese]. <i>Acta Scientiae Veterinariae</i> . 2018. 46 (Supplement) (no pagination):#pages#	One or more exclusion criteria
L1	Narwaria, Y. S.,Saksena, D. N.. Acute toxicity bioassay and behavioural responses induced by sodium fluoride in	One or more exclusion criteria

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L1	Lisova, K., Wang, J., Rios, A., Van Dam, R. M.. Adaptation and optimization of [¹⁸ F] Florbetaben ([¹⁸ F]FBB) radiosynthesis to a microdroplet reactor. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2019. 62 (Supplement 1):S353-S354	One or more exclusion criteria
L1	Buckley, H. L., Molla, N. J., Cherukumilli, K., Boden, K. S., Gadgil, A. J.. Addressing technical barriers for reliable, safe removal of fluoride from drinking water using minimally processed bauxite ores. <i>Dev Eng</i> . 2018. 3:175-187	One or more exclusion criteria
L1	Fromme, H., Wöckner, M., Roscher, E., Völkel, W.. ADONA and perfluoroalkylated substances in plasma samples of German blood donors living in South Germany. <i>Int J Hyg Environ Health</i> . 2017. 220:455-460	One or more exclusion criteria
L1	Daifullah, A. A., Yakout, S. M., Elreefy, S. A.. Adsorption of fluoride in aqueous solutions using KMnO ₄ -modified activated carbon derived from steam pyrolysis of rice straw. <i>Journal of Hazardous Materials</i> . 2007. 147:633-43	One or more exclusion criteria
L1	Viberg, H., Lee, I., Eriksson, P.. Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. <i>Toxicology</i> . 2013. 304:185-91	One or more exclusion criteria
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. <i>Br J Psychiatry</i> . 2011. 199:187-93	One or more exclusion criteria

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L1	Johnson, J. K., Hoffman, C. M., Jr., Smith, D. A., Xia, Z.. Advanced Filtration Membranes for the Removal of Perfluoroalkyl Species from Water. <i>ACS Omega</i> . 2019. 4:8001-8006	One or more exclusion criteria
L1	He, P., Haswell, S. J., Pamme, N., Archibald, S. J.. Advances in processes for PET radiotracer synthesis: separation of [¹⁸ F]fluoride from enriched [¹⁸ O]water. <i>Appl Radiat Isot</i> . 2014. 91:64-70	One or more exclusion criteria
L1	Levine, R.. Advancing the scientific basis of oral health education. <i>Community Dent Health</i> . 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 (<i>Rhinella arenarum</i>) tadpoles. <i>Environmental Monitoring and Assessment</i> . 2016. 188 (8) (no pagination):#pages#	One or more exclusion criteria
L1	Dahi, E.. Africa's U-turn in defluoridation policy: From the Nalgonda technique to bone char. <i>Fluoride</i> . 2016. Part 1. 49:401-416	One or more exclusion criteria
L1	Shashi, A., Kumar, M.. Age specific fluoride exposure in drinking water - A clinical multiparametric study. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences</i> . 2008. 10:655-660	One or more exclusion criteria
L1	Abtahi, M., Dobaradaran, S., Jorfi, S., Koolivand, A., Mohebbi, M. R., Montazeri, A., Khaloo, S. S., Keshmiri, S., Saeedi, R.. Age-sex specific and sequela-specific disability-adjusted life years (DALYs) due to dental caries preventable through water fluoridation: An assessment at the national and subnational levels in Iran, 2016. <i>Environ Res</i> . 2018.	One or more exclusion criteria

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L1	Abtahi, M.,Dobaradaran, S.,Jorfi, S.,Koolivand, A.,Khaloo, S. S.,Spitz, J.,Saeedi, H.,Golchinpour, N.,Saeedi, R.. Age-sex specific disability-adjusted life years (DALYs) attributable to elevated levels of fluoride in drinking water: A national and subnational study in Iran, 2017. <i>Water Res.</i> 2019. 157:94-105	One or more exclusion criteria
L1	Bassin, E. B.,Wypij, D.,Davis, R. B.,Mittleman, M. A.. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). <i>Cancer Causes Control.</i> 2006. 17:421-8	One or more exclusion criteria
L1	Arulkumar, M.,Vijayan, R.,Penislusshiyam, S.,Sathishkumar, P.,Angayarkanni, J.,Palvannan, T.. Alteration of paraoxonase, arylesterase and lactonase activities in people around fluoride endemic area of Tamil Nadu, India. <i>Clinica Chimica Acta.</i> 2017. 471:206-215	One or more exclusion criteria
L1	Randhawa, S. S.,Sharma, S.,Ranjan, R.. Alterations in blood concentrations of macro- and microminerals in water buffaloes living in endemic fluorosis areas of Punjab. <i>Fluoride.</i> 2012. 45 (3 PART 1):190-191	One or more exclusion criteria
L1	Ma, S. K.,Bae, E. H.,Kim, I. J.,Choi, C.,Lee, J.,Kim, S. W.. Altered renal expression of aquaporin water channels and sodium transporters in rats with two-kidney, one-clip hypertension. <i>Kidney Blood Press Res.</i> 2009. 32:411-20	One or more exclusion criteria
L1	Russ, T. C.,Killin, L. O. J.,Hannah, J.,Batty, G. D.,Deary, I. J.,Starr, J. M.. Aluminium and fluoride in drinking water in relation to later dementia risk. <i>British Journal of Psychiatry.</i> 2020. 216:29-34	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. <i>J Alzheimers Dis.</i> 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. <i>Journal of Toxicology.</i> 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. <i>Toxicology and Environmental Health Sciences.</i> 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, R. A.. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. <i>Ca-A Cancer Journal for Clinicians.</i> 2006. 56:254-281	One or more exclusion criteria
L1	Sun, L.,Gao, Y.,Liu, H.,Zhang, W.,Ding, Y.,Li, B.,Li, M.,Sun, D.. An assessment of the relationship between excess fluoride intake from drinking water and essential	One or more exclusion criteria

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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 NaYF ₄ nanoparticles in buffers and biological growth media for biolabeling applications. <i>Langmuir</i> . 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. <i>Ann Nucl Med</i> . 2010. 24:149-55	One or more exclusion criteria
L1	Erickson, J. D.. An epidemiologic enterprise: From fluoride to folate. <i>Birth Defects Research Part A - Clinical and Molecular Teratology</i> . 2012. 94 (5):292	One or more exclusion criteria
L1	Zhai, L.,Wang, X.,Gao, H.,Li, L.,Lu, X.,Li, H.,Chen, P.. An epidemiological investigation of endemic fluorosis in Shandong Province in 2013. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2015. 34:508-510	One or more exclusion criteria
L1	Harinath, B.. An epidemiological study of dental fluorosis among higher secondary school children belonging to an endemic rural area in Nalgonda district, Andhra Pradesh. <i>Australasian Medical Journal</i> . 2012. 5 (1):42-43	One or more exclusion criteria
L1	Nirgude, A. S.,Saiprasad, G. S.,Naik, P. R.,Mohanty, S.. An epidemiological study on fluorosis in an urban slum area of Nalgonda, Andhra Pradesh, India. <i>Indian Journal of Public</i>	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. <i>Journal of Environmental Management</i> . 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. <i>J Dent</i> . 2012. 40:585-93	One or more exclusion criteria
L1	Koletsis-Kounari, H.,Mamai-Homata, E.,Diamanti, I.. An in vitro study of the effect of aluminum and the combined effect of strontium, aluminum, and fluoride elements on early enamel carious lesions. <i>Biological Trace Element Research</i> . 2012. 147:418-427	One or more exclusion criteria
L1	Vivar, M.,Pichel, N.,Fuentes, M.,Martínez, F.. An insight into the drinking-water access in the health institutions at the Saharawi refugee camps in Tindouf (Algeria) after 40years of conflict. <i>Sci Total Environ</i> . 2016. 550:534-546	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2014. 33:174-177	One or more exclusion criteria

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L1	Honkanen, I.,Hock, L.,Bettendorf, B.,Fiordellisi, W.. An unlikely source of periostitis. <i>Journal of General Internal Medicine</i> . 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. <i>Turkish Journal of Gastroenterology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2013. 32:408-411	One or more exclusion criteria
L1	Jia, L. H.,Ma, J.,Du, Y. G.,Ma, D. R.,Liang, S. L.,Zhou, C. H.. Analysis of an investigational result of drinking-water-borne endemic fluorosis in Hebei Province in 2010. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2013. 32:659-661	One or more exclusion criteria
L1	Jameel, R. A.,Khan, S. S.,Rahim, Z. H. A.,Bakri, M. M.,Siddiqui, S.. Analysis of dental erosion induced by different beverages and validity of equipment for identifying early dental erosion, in vitro study. <i>Journal of the Pakistan Medical Association</i> . 2016. 66:843-848	One or more exclusion criteria
L1	Gao, R. P.,Xu, Y.. Analysis of disease surveillance of endemic fluorosis in Yanqing county of Beijing in 2008. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:176-178	One or more exclusion criteria
L1	Liu, X. H.,Hu, R. C.,Zheng, C. S.,Zhou, M. R.,Jiang, Z. L.,Tian, S. C.,Gai, C. C.,Zhang, X. K.. Analysis of endemic fluorosis of Xinbaerhuyouqi in Hulunbeir city of Inner	One or more exclusion criteria

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L1	Kataria, H. C.,Bux, S.,Ambhore, S.,Shrivastava, S. C.,Pathak, G.,Namdeo, M.. Analysis of fluoride concentration in groundwater in and around Bhopal city. M.P. India. <i>Biosciences Biotechnology Research Asia</i> . 2008. 5:699-700	One or more exclusion criteria
L1	Niu, Z. H.,Zhao, J. L.. Analysis of monitoring data of drinking-water borne endemic fluorosis in Xinzhou of Shanxi province in 2010. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:321-324	One or more exclusion criteria
L1	Ge, S. Z. G.. Analysis of monitoring results of drinking-tea borne endemic fluorosis in Lhasa of Tibet. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:325-328	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.. Analysis of monitoring results of endemic fluorosis in Shandong province in 2009. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:188-193	One or more exclusion criteria
L1	Li, P.,Wang, Z.,Wu, Z.. Analysis of monitoring results of fluoride-safe water supply projects in drinking water type of fluorosis and arsenic poisoning areas in Shanxi Province in 2012. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2015. 34:116-118	One or more exclusion criteria

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L1	Mahajan, R. K.,Walia, T. P.,Lark, B. S.,Sumanjit,. Analysis of physical and chemical parameters of bottled drinking water. <i>Int J Environ Health Res.</i> 2006. 16:89-98	One or more exclusion criteria
L1	Chen, P. Z.,Yun, Z. J.,Li, H. X.,Gao, H. X.,Wang, Y. T.,Gao, J.,Yin, Y. Y.. Analysis of surveillance outcome of endemic fluorosis in Shandong province in 2010. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2012. 31:191-193	One or more exclusion criteria
L1	Wei, S. Y.,He, D. L.,Ding, P.,Pu, G. L.,Lu, Q.,Yang, P.,Zhou, M.,Han, W.,Tan, D. F.,Xi, G. X.,Pu, W. Q.. Analysis of surveillance results of drinking water type of endemic fluorosis in Qinghai province in 2009. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2011. 30:542-545	One or more exclusion criteria
L1	Shu, C. L.,Wang, C. S.,Wang, Y.,Xia, Y. T.,Chen, S. H.. Analysis of surveillance results of drinking-water-borne endemic fluorosis in Jiangsu Province in 2009. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2013. 32:662-667	One or more exclusion criteria
L1	Yun, Z. J.,Chen, P. Z.,Bian, J. C.,Wang, Y. T.,Li, H. X.,Liu, Y.. Analysis of survey results of endemic fluorosis in Shandong province in 2008. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2011. 30:51-55	One or more exclusion criteria
L1	Zhang, L.,Yang, Z. M.,Wu, Z. J.,Luo, Z. Y.,Yan, Q.,Zhang, J.. Analysis of the survey result of the coal-burning endemic fluorosis in Hongya County of Sichuan Province in 2006. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2008. 27:191-193	One or more exclusion criteria
L1	Chen, P. Z.,Yun, Z. J.,Bian, J. C.,Li, H. X.,Ma, A. H.,Gao, H. X.,Wang, Y. T.,Zhao, L. J.. Analysis on surveillance outcome of endemic fluorosis in Shandong Province from	One or more exclusion criteria

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L1	Shen, Y. F.,Han, H. P.,Xiu, C. P.,Sun, D. J.. Analysis on the present running status of water-improving project in Anda city, Heilonjiang province in 2008. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:319-321	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 <i>Kobus ellipsiprymnus defassa</i> (Ruppel 1835). <i>Archives of Environmental Contamination and Toxicology</i> . 2007. 52:270-281	One or more exclusion criteria
L1	Gutierrez, R. M. P.,Hoyo-Vadillo, C.. Anti-inflammatory Potential of <i>Petiveria alliacea</i> on Activated RAW264.7 Murine Macrophages. <i>Pharmacogn Mag</i> . 2017. 13:S174-s178	One or more exclusion criteria
L1	Shinonaga, Y.,Arita, K.. Antibacterial effect of acrylic dental devices after surface modification by fluorine and silver dual-ion implantation. <i>Acta Biomater</i> . 2012. 8:1388-93	One or more exclusion criteria

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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. <i>Environmental Toxicology & Pharmacology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2010. 29:544-546	One or more exclusion criteria
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L1	Rezaee, R.,Mahvi, A. H.,Maleki, A.,Jafari, A.,Ashrafi, S. D.,Safari, M.. Application of modified wheat straw for fluoride reduction from aqueous solutions: Isotherms and kinetics. <i>Fluoride</i> . 2012. 45 (3 PART 1):195	One or more exclusion criteria
L1	Shukurov, R.,Balashov, M.,Dadashov, Z.,Valiyev, M.,Mehdi, E.,Novruzov, F.. Application of production and quality control procedures of 18F-PSMA-1007: Dominant in	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. <i>Molecular Imaging and Biology. Conference</i> . 2014. 17:#pages#	One or more exclusion criteria
L1	Marghade, D.,Malpe, D. B.,Subba Rao, N.. Applications of geochemical and multivariate statistical approaches for the evaluation of groundwater quality and human health risks in a semi-arid region of eastern Maharashtra, India. <i>Environ Geochem Health</i> . 2019. #volume#:#pages#	One or more exclusion criteria
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. <i>Environ Geochem Health</i> . 2009. 31:643-55	One or more exclusion criteria
L1	Ericson, B.,Caravanos, J.,Chatham-Stephens, K.,Landrigan, P.,Fuller, R.. Approaches to systematic assessment of environmental exposures posed at hazardous waste sites in the developing world: The Toxic Sites Identification Program. <i>Environmental Monitoring and Assessment</i> . 2013. 185:1755-1766	One or more exclusion criteria
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.	One or more exclusion criteria

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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. <i>Environmental Monitoring and Assessment</i> . 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?. <i>Journal of Immunotoxicology</i> . 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 study of GP practice data and fluoride levels in drinking water. <i>J Epidemiol Community Health</i> . 2015. 69:619-24	One or more exclusion criteria
L1	Newton, J. N.,Verne, J.,Dancox, M.,Young, N.. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? Comments on the authors' response to earlier criticism. <i>J Epidemiol Community Health</i> . 2017. 71:315-316	One or more exclusion criteria
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. <i>Toxicol Ind Health</i> . 2017. 33:655-672	One or more exclusion criteria
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	and fluoride co-contamination in shallow aquifers from agricultural suburbs and an industrial area of Punjab, Pakistan: Spatial trends, sources and human health implications. <i>Toxicology & Industrial Health</i> . 2017. 33:655-672	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. <i>Mutat Res Genet Toxicol Environ Mutagen</i> . 2014. 761:27-34	One or more exclusion criteria
L1	Jadhav, S. V.,Bringas, E.,Yadav, G. D.,Rathod, V. K.,Ortiz, I.,Marathe, K. V.. Arsenic and fluoride contaminated groundwaters: A review of current technologies for contaminants removal. <i>J Environ Manage</i> . 2015. 162:306-25	One or more exclusion criteria
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. <i>Environmental Health Perspectives</i> . 2007. 115:643-647	One or more exclusion criteria
L1	Chouhan, S.,Flora, S. J.. Arsenic and fluoride: two major ground water pollutants. <i>Indian Journal of Experimental Biology</i> . 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	One or more exclusion criteria

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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. <i>Environmental Health Perspectives</i> . 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 single-source methods to a probabilistic multi-exposure-pathway approach. <i>Environment International</i> . 2014. 68:192-199	One or more exclusion criteria
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. <i>International Research Journal of Pharmacy</i> . 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 <i>Hypsiboas cordobae</i> (Barrio 1965) inhabiting aquatic ecosystems associated to fluorite mine. <i>Ecotoxicol Environ Saf</i> . 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. <i>Journal of Pharmacy Research</i> . 2017. 11:1209-1213	One or more exclusion criteria
L1	Sarinana-Ruiz, Y. A.,Vazquez-Arenas, J.,Sosa-Rodriguez,	One or more exclusion

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L1	Sariñana-Ruiz, Y. A.,Vazquez-Arenas, J.,Sosa-Rodríguez, F. S.,Labastida, I.,Armienta, M. A.,Aragón-Piña, A.,Escobedo-Bretado, M. A.,González-Valdez, L. S.,Ponce-Peña, P.,Ramírez-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. <i>Chemosphere</i> . 2017. 178:391-401	One or more exclusion criteria
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. <i>Environ Sci Pollut Res Int</i> . 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. <i>J Ethnopharmacol</i> . 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. <i>Food Chem Toxicol</i> . 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	One or more exclusion criteria

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L1	Dutta, J.. Assessment of fluoride, arsenic and other heavy metals in the ground water of tea gardens belt of Sonitpur district, Assam, India. <i>International Journal of ChemTech Research.</i> 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. <i>Environmental Monitoring & Assessment.</i> 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. <i>Int J Environ Res Public Health.</i> 2019. 16:#pages#	One or more exclusion criteria
L1	Ranjan, S.,Yasmin, S.. Assessment of groundwater quality in Gaya region with respect to fluoride. <i>Journal of Ecophysiology and Occupational Health.</i> 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 secondary pollution on the example of Kazan. <i>Research</i>	One or more exclusion criteria

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	<i>Journal of Pharmaceutical, Biological and Chemical Sciences</i> . 2016. 7:1114-1117	
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. <i>PLoS ONE</i> . 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. <i>Environ Geochem Health</i> . 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. <i>Amyotrophic Lateral Sclerosis</i> . 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. <i>Environmental Monitoring and Assessment</i> . 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. <i>Environ Sci Pollut Res Int</i> . 2017. 24:20300-20314	One or more exclusion criteria
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.	One or more exclusion criteria

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L1	Rawlani, S.,Rawlani, S.,Rawlani, S.. Assessment of Skeletal and Non-skeletal Fluorosis in Endemic Fluoridated Areas of Vidharbha Region, India: A Survey. <i>Indian Journal of Community Medicine</i> . 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. <i>Asian Journal of Pharmaceutical and Clinical Research</i> . 2017. 10:322-325	One or more exclusion criteria
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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. <i>Ecotoxicol Environ Saf</i> . 2013. 96:32-40	One or more exclusion criteria
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L1	Cherry, D. C.,Huggins, B.,Gilmore, K.. Children's Health in the Rural Environment. <i>Pediatric Clinics of North America</i> . 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 isotopic ratio DELTA ⁵³ Cr/DELTA ⁵² Cr, geochemical and geostatistical modelling. <i>Chemosphere</i> . 2019. 220:943-953	One or more exclusion criteria
L1	Buscariolo, I. A.,Penha, S. S.,Rocha, R. G.. Chronic fluorine intoxication. Prevalence of dental fluorosis in schoolchildren. [Portuguese]. <i>Revista de Ciencias Farmaceuticas Basica e Aplicada</i> . 2006. 27:83-87	One or more exclusion criteria
L1	Kurdi, M. S.. Chronic fluorosis: The disease and its anaesthetic implications. <i>Indian Journal of Anaesthesia</i> . 2016. 60:157-162	One or more exclusion criteria
L1	Jayasinghe, S.,Zhu, Y. G.. Chronic kidney disease of unknown etiology (CKDu): Using a system dynamics model to conceptualize the multiple environmental causative pathways of the epidemic. <i>Science of the Total Environment</i> . 2020. 705 (no pagination):#pages#	One or more exclusion criteria
L1	Dharma-Wardana, M. W. C.. Chronic kidney disease of unknown etiology and the effect of multiple-ion interactions. <i>Environ Geochem Health</i> . 2018. 40:705-719	One or more exclusion criteria

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L1	Chandrajith, R.,Nanayakkara, S.,Itai, K.,Aturaliya, T. N.,Dissanayake, C. B.,Abeysekera, T.,Harada, K.,Watanabe, T.,Koizumi, A.. Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. <i>Environ Geochem Health</i> . 2011. 33:267-78	One or more exclusion criteria
L1	Bandara, J. M.,Senevirathna, D. M.,Dasanayake, D. M.,Herath, V.,Bandara, J. M.,Abeysekara, T.,Rajapaksha, K. H.. Chronic renal failure among farm families in cascade irrigation systems in Sri Lanka associated with elevated dietary cadmium levels in rice and freshwater fish (Tilapia). <i>Environ Geochem Health</i> . 2008. 30:465-78	One or more exclusion criteria
L1	Carstairs, C.. Cities without cavities: democracy, risk, and public health. <i>J Can Stud</i> . 2010. 44:146-70	One or more exclusion criteria
L1	Ipci, S. D.,Cakar, G.,Kuru, B.,Yilmaz, S.. Clinical evaluation of lasers and sodium fluoride gel in the treatment of dentine hypersensitivity. <i>Photomed Laser Surg</i> . 2009. 27:85-91	One or more exclusion criteria
L1	Lee, S. H. O.,Lee, N. Y.,Lee, I. N. H.. Clinical evaluation of the efficacy of fluoride adhesive tape (F-PVA) in reducing dentin hypersensitivity. <i>American Journal of Dentistry</i> . 2013. 26:143-148	One or more exclusion criteria
L1	Lee, S. H.,Lee, N. Y.,Lee, I. H.. Clinical evaluation of the efficacy of fluoride adhesive tape (F-PVA) in reducing dentin hypersensitivity. <i>Am J Dent</i> . 2013. 26:143-8	One or more exclusion criteria
L1	Dixit, M.,Saxena, P.,Verma, S.,Kumari, S.,Kheruka, S.,Verma, R. S.,Gambhir, S.. Clinical grade automated synthesis of fluorodeoxyglucose [¹⁸ F] FDG at newly established cyclotron facility at SGPGIMS, Lucknow.	One or more exclusion criteria

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L1	Bouyeure-Petit, A. C.,Chastan, M.,Edet-Sanson, A.,Becker, S.,Thureau, S.,Houivet, E.,Vera, P.,Hapdey, S.. Clinical respiratory motion correction software (reconstruct, register and averaged-RRA), for (18)F-FDG-PET-CT: phantom validation, practical implications and patient evaluation. <i>Br J Radiol</i> . 2017. 90:20160549	One or more exclusion criteria
L1	Rasool, A.,Xiao, T.,Baig, Z. T.,Masood, S.,Mostofa, K. M.,Iqbal, M.. Co-occurrence of arsenic and fluoride in the groundwater of Punjab, Pakistan: source discrimination and health risk assessment. <i>Environ Sci Pollut Res Int</i> . 2015. 22:19729-46	One or more exclusion criteria
L1	Coyte, R. M.,Singh, A.,Furst, K. E.,Mitch, W. A.,Vengosh, A.. Co-occurrence of geogenic and anthropogenic contaminants in groundwater from Rajasthan, India. <i>Sci Total Environ</i> . 2019. 688:1216-1227	One or more exclusion criteria
L1	Alarcón-Herrera, M. T.,Martin-Alarcon, D. A.,Gutiérrez, M.,Reynoso-Cuevas, L.,Martín-Domínguez, A.,Olmos-Márquez, M. A.,Bundschuh, J.. Co-occurrence, possible origin, and health-risk assessment of arsenic and fluoride in drinking water sources in Mexico: Geographical data visualization. <i>Sci Total Environ</i> . 2020. 698:134168	One or more exclusion criteria
L1	Navi, M.,Skelly, C.,Taulis, M.,Nasiri, S.. Coal seam gas water: Potential hazards and exposure pathways in Queensland. <i>International Journal of Environmental Health Research</i> . 2015. 25:162-183	One or more exclusion criteria
L1	Chen, J.,Liu, G.,Kang, Y.,Wu, B.,Sun, R.,Zhou, C.,Wu, D..	One or more exclusion

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	Coal utilization in China: environmental impacts and human criteria health. <i>Environ Geochem Health</i> . 2014. 36:735-53	
L1	Li, M.,Gao, Y.,Cui, J.,Li, Y.,Li, B.,Liu, Y.,Sun, J.,Liu, X.,Liu, H.,Zhao, L.,Sun, D.. Cognitive Impairment and Risk Factors in Elderly People Living in Fluorosis Areas in China. <i>Biol Trace Elem Res</i> . 2016. 172:53-60	One or more exclusion criteria
L1	Tang, L.,Wang, L. J.,Zhang, Y. L.,Bai, S. B.,Zhong, J. J.,Zhang, Y. X.,Liu, K. T.. COLIXA3 gene expression of peripheral blood lymphocyte in patients with endemic fluorosis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:144-146	One or more exclusion criteria
L1	Escobar-García, D.,Mejía-Saavedra, J.,Jarquín-Yáñez, L.,Molina-Frechero, N.,Pozos-Guillén, A.. Collagenase 1A2 (COL1A2) gene A/C polymorphism in relation to severity of dental fluorosis. <i>Community Dent Oral Epidemiol</i> . 2016. 44:162-8	One or more exclusion criteria
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L1	Rango, T.,Colombani, N.,Mastrocicco, M.,Bianchini, G.,Beccaluva, L.. Column elution experiments on volcanic ash: Geochemical implications for the main Ethiopian rift waters. <i>Water, Air, and Soil Pollution</i> . 2010. 208:221-233	One or more exclusion criteria
L1	Mittal, M.,Chatterjee, S.,Flora, S. J. S.. Combination therapy with vitamin C and DMSA for arsenic-fluoride co-exposure in rats. <i>Metallomics : Integrated Biometal</i>	One or more exclusion criteria

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L1	Moolenburgh, H.. Comment on editorial report: Medline again rejects Fluoride. <i>Fluoride</i> . 2010. 43:81-84	One or more exclusion criteria
L1	Sun, D.. Commentary. <i>Journal of Neurosciences in Rural Practice</i> . 2012. 3:149-150	One or more exclusion criteria
L1	Grimes, D. R.. Commentary on "Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water". <i>J Epidemiol Community Health</i> . 2015. 69:616	One or more exclusion criteria
L1	Montgomery, J.. Commentary on "Public health, private right and the common law". <i>Public Health</i> . 2006. 120:50-51	One or more exclusion criteria
L1	Paul, C. J.,Jeuland, M. A.,Godebo, T. R.,Weinthal, E.. Communities coping with risks: Household water choice and environmental health in the Ethiopian Rift Valley. <i>Environmental Science and Policy</i> . 2018. 86:85-94	One or more exclusion criteria
L1	Young, N.,Newton, J.,Morris, J.,Morris, J.,Langford, J.,Iloya, J.,Edwards, D.,Makhani, S.,Verne, J.. Community water fluoridation and health outcomes in England: a cross-sectional study. <i>Community Dent Oral Epidemiol</i> . 2015. 43:550-9	One or more exclusion criteria
L1	Till, C.,Green, R.,Grundy, J. G.,Hornung, R.,Neufeld, R.,Martinez-Mier, E. A.,Ayotte, P.,Muckle, G.,Lanphear, B.. Community water fluoridation and urinary fluoride concentrations in a national sample of pregnant women in Canada. <i>Environmental Health Perspectives</i> . 2018. 126 (10) (no pagination):#pages#	One or more exclusion criteria

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L1	Wang, L. F.,Chen, Q.,Long, X. P.,Wu, X. B.,Sun, L.. Comparative analysis of groundwater fluorine levels and other characteristics in two areas of Laizhou Bay and its explanation on fluorine enrichment. <i>Water Science and Technology: Water Supply.</i> 2015. 15:384-394	One or more exclusion criteria
L1	Aparna, S.,Setty, S.,Thakur, S.. Comparative efficacy of two treatment modalities for dentinal hypersensitivity: a clinical trial. <i>Indian J Dent Res.</i> 2010. 21:544-8	One or more exclusion criteria
L1	Ramesh, M.,Malathi, N.,Ramesh, K.,Aruna, R.,Kuruvilla, S.. Comparative evaluation of dental and skeletal fluorosis in an endemic fluorosed district, Salem, Tamil Nadu. <i>Journal of Pharmacy and Bioallied Sciences.</i> 2017. 9:S88-S91	One or more exclusion criteria
L1	Rikame, V.,Doshi, Y.,Horowitz, R. A.,Kevadia-Shah, V.,Shah, M.. Comparative Evaluation of Fluoridated Mouthwash and Sodium Bicarbonate in Management of Dentin Hypersensitivity: An In Vitro SEM Study. <i>Compend Contin Educ Dent.</i> 2018. 39:e5-e8	One or more exclusion criteria

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L1	Pandit, N.,Gupta, R.,Bansal, A.. Comparative evaluation of two commercially available desensitizing agents for the treatment of dentinal hypersensitivity. <i>Indian J Dent Res</i> . 2012. 23:778-83	One or more exclusion criteria
L1	Sheng, N.,Zhou, X.,Zheng, F.,Pan, Y.,Guo, X.,Guo, Y.,Sun, Y.,Dai, J.. Comparative hepatotoxicity of 6:2 fluorotelomer carboxylic acid and 6:2 fluorotelomer sulfonic acid, two fluorinated alternatives to long-chain perfluoroalkyl acids, on adult male mice. <i>Arch Toxicol</i> . 2017. 91:2909-2919	One or more exclusion criteria
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L1	Qian, W. W.,Lin, J. H.,Hu, Y.. Comparative study on effect of different remineralization agents on eroded primary teeth enamel. [Chinese]. <i>Journal of Shanghai Jiaotong University (Medical Science)</i> . 2014. 34:1126-1131	One or more exclusion criteria
L1	Choi, Y. E.,Seo, D. Y.,Lee, J. E.,Ha, Y.,Park, A. H.,Jeong, J. W.,Kwon, O. W.,Kim, Y. J.. Comparative toxicity of Perfluorooctanesulfonic acid (PFOS) and Perfluorooctanesulfonamide (PFOSA) in fish hepatoma cell line, PLHC-1. <i>Toxicology and Environmental Health Sciences</i> . 2018. 10 (4):S58	One or more exclusion criteria
L1	Solis-Angeles, S.,Cardenas Gonzalez, M.,Jimenez-Cordova, M. I.,Villarreal-Vega, E.,Aguilar-Madrid, G.,Gonzalez-Horta, M. C.,Del Razo, L. M.,Barbier, O.. Comparative urinary miRNAs expression and cystatin C level in adults chronically exposed to fluoride through drinking water. <i>Toxicology Letters</i> . 2016. 259 (Supplement 1):S115	One or more exclusion criteria
L1	Datturi, S.,Steenbergen, F. V.,Beusekom, M. V.,Kebede, S.. Comparing defluoridation and safe sourcing for fluorosis mitigation in the ethiopian central rift valley. <i>Fluoride</i> . 2015. 48:293-314	One or more exclusion criteria
L1	Nicole, W.. Comparing fluoride exposures in pregnant canadian women: Fluoridated versus nonfluoridated drinking water. <i>Environmental Health Perspectives</i> . 2019. 127 (7) (no pagination):#pages#	One or more exclusion criteria
L1	Bozorgi, M.,Ghasempour, M.,Ahmadi, G.,Khafri, S..	One or more exclusion

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	Comparison between the effects of green and black tea, and fluoride on microhardness and prevention of demineralization of deciduous teeth enamel. <i>Journal of Babol University of Medical Sciences</i> . 2018. 20:14-19	criteria
L1	Gao, J.,Yun, Z. J.,Chen, P. Z.,Bian, J. C.,Wang, Y. T.,Li, H. X.,Gao, H. X.,Ma, A. H.. Comparison of body fluorine levels in Liangshan and Boxing counties of Shandong province from 2007 to 2009. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:199-201	One or more exclusion criteria
L1	Pradeep, A. R.,Agarwal, E.,Naik, S. B.,Bajaj, P.,Kalra, N.. Comparison of efficacy of three commercially available dentifrices [corrected] on dentinal hypersensitivity: a randomized clinical trial. <i>Aust Dent J</i> . 2012. 57:429-34	One or more exclusion criteria
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L1	Takei, M.,Sakae, T.,Mishima, H.,Yoshikawa, M.. Comparison of harmfulness between fluoride and cadmium ions on the crystal nucleation process. <i>Bone</i> . 2009. 2):S414	One or more exclusion criteria
L1	Hirzy, J. W.,Carton, R. J.,Bonanni, C. D.,Montanero, C. M.,Nagle, M. F.. Comparison of hydrofluorosilicic acid and pharmaceutical sodium fluoride as fluoridating agents-A cost-benefit analysis. <i>Environmental Science and Policy</i> . 2013. 29:81-86	One or more exclusion criteria
L1	Yu, Q.,Liu, H.,Liu, Z.,Peng, Y.,Cheng, X.,Ma, K.,Ji, Y.. Comparison of nanofluoridated hydroxyapatite of varying	One or more exclusion criteria

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L1	Usuda, K.,Kono, R.,Ueno, T.,Ito, Y.,Dote, T.,Yokoyama, H.,Kono, K.,Tamaki, J.. Comparison of the Biological Impacts of the Fluoride Compounds by Graphical Risk Visualization Map Technique. <i>Biol Trace Elem Res.</i> 2015. 167:84-90	One or more exclusion criteria
L1	Sun, X. G.,Huang, G.,Liu, J. J.,Wan, L. R.. Comparison of the effect of positive and negative oral contrast agents on (18)F-FDG PET/CT scan. <i>Hell J Nucl Med.</i> 2009. 12:115-8	One or more exclusion criteria
L1	Rice, J. R.,Boyd, W. A.,Chandra, D.,Smith, M. V.,Besten, P. K. D.,Freedman, J. H.. Comparison of the toxicity of fluoridation compounds in the nematode <i>Caenorhabditis elegans</i> . <i>Environmental Toxicology and Chemistry.</i> 2014. 33:82-88	One or more exclusion criteria
L1	Shorter, J. P.,Massawe, J.,Parry, N.,Walker, R. W.. Comparison of two village primary schools in northern Tanzania affected by fluorosis. <i>International Health.</i> 2010. 2:269-74	One or more exclusion criteria
L1	Wu, K.,Zhang, N.,Liu, T.,Ma, C.,Jin, P.,Zhang, F.,Zhang, J.,Wang, X.. Competitive adsorption behaviors of arsenite and fluoride onto manganese-aluminum binary adsorbents. <i>Colloids and Surfaces A: Physicochemical and Engineering Aspects.</i> 2017. 529:185-194	One or more exclusion criteria
L1	Murtaza, B.,Natasha,,Amjad, M.,Shahid, M.,Imran, M.,Shah, N. S.,Abbas, G.,Naeem, M. A.,Amjad, M.. Compositional and health risk assessment of drinking water from health facilities of District Vehari, Pakistan. <i>Environ</i>	One or more exclusion criteria

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L1	Fantong, W. Y.,Jokam Nenkam, T. L. L.,Nbendah, P.,Kimbi, S. B.,Fru, E. C.,Kamtchueng, B. T.,Takoundjou, A. F.,Tejiobou, A. R.,Ngueutchoua, G.,Kringel, R.. Compositions and mobility of major, deltaD, delta ¹⁸ O, trace, and REEs patterns in water sources at Benue River Basin-Cameroon: implications for recharge mechanisms, geo-environmental controls, and public health. <i>Environmental geochemistry and health</i> .. 2020. 28:#pages#	One or more exclusion criteria
L1	Zong, Y.,Shea, C.,Maffucci, K.,Ojima, I.. Computational Design and Synthesis of Novel Fluoro-Analogs of Combretastatins A-4 and A-1. <i>J Fluor Chem</i> . 2017. 203:193-199	One or more exclusion criteria
L1	Pollick, H. F.. Concerns about water fluoridation, IQ, and osteosarcoma lack credible evidence. <i>Int J Occup Environ Health</i> . 2006. 12:91-94	One or more exclusion criteria
L1	Bachanek, T.,Hendzel, B.,Wolańska, E.,Samborski, D.,Jarosz, Z.,Pitura, K. M.,Dzida, K.,Podymniak, M.,Tymczyzna-Borowicz, B.,Niewczas, A.,Shybinskyy, V.,Zimenkovsky, A.. 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. <i>Ann Agric Environ Med</i> . 2019. 26:623-629	One or more exclusion criteria
L1	Coplan, M. J.,Patch, S. C.,Masters, R. D.,Bachman, M. S.. Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals. <i>NeuroToxicology</i> .	One or more exclusion criteria

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L1	Wang, M.,Svatunek, D.,Rohlfing, K.,Liu, Y.,Wang, H.,Giglio, B.,Yuan, H.,Wu, Z.,Li, Z.,Fox, J.. Conformationally Strained trans-Cyclooctene (sTCO) Enables the Rapid Construction of (18)F-PET Probes via Tetrazine Ligation. <i>Theranostics</i> . 2016. 6:887-95	One or more exclusion criteria
L1	Sankararamakrishnan, N.,Sharma, A. K.,Iyengar, L.. Contamination of nitrate and fluoride in ground water along the Ganges Alluvial Plain of Kanpur district, Uttar Pradesh, India. <i>Environmental Monitoring and Assessment</i> . 2008. 146:375-382	One or more exclusion criteria
L1	Peters, M.,Guo, Q.,Strauss, H.,Wei, R.,Li, S.,Yue, F.. Contamination patterns in river water from rural Beijing: A hydrochemical and multiple stable isotope study. <i>Science of the Total Environment</i> . 2019. 654:226-236	One or more exclusion criteria
L1	Weegman, B. P.,Einstein, S. A.,Steyn, L. V.,Suszynski, T. M.,Firpo, M. T.,Graham, M. L.,Janacek, J.,Eberly, L. E.,Garwood, M.,Papas, K. K.. Continuous oxygen delivery improves oxygenation of tissue-engineered islet grafts in vivo as measured with fluorine-19 magnetic resonance spectroscopy. <i>Xenotransplantation</i> . 2015. 1):S128-S129	One or more exclusion criteria
L1	Kaseva, M. E.. Contribution of trona (magadi) into excessive fluorosis-a case study in Maji ya Chai ward, northern Tanzania. <i>Science of the Total Environment</i> . 2006. 366:92-100	One or more exclusion criteria
L1	Yun, Z.,Yin, Y.,Gao, J.,Wen, Y.,Bian, J.,Chen, P.,Wang, Y.. Control status quo of drinking-water-borne endemic fluorosis in the disease affected areas in Shandong	One or more exclusion criteria

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	Province in 2012: An analysis of survey results. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2014. 33:155-159	
L1	Fookes, F. A., Mengatto, L. N., Rigalli, A., Luna, J. A.. Controlled fluoride release for osteoporosis treatment using orally administered chitosan hydrogels. <i>Journal of Drug Delivery Science and Technology</i> . 2019. 51:268-275	One or more exclusion criteria
L1	Hirakawa, K., Suzuki, A., Ouyang, D., Okazaki, S., Ibuki, Y., Nakazaki, J., Segawa, H.. Controlled Photodynamic Action of Axial Fluorinated DiethoxyP(V)tetrakis(p-methoxyphenyl)porphyrin through Self-Aggregation. <i>Chem Res Toxicol</i> . 2019. 32:1638-1645	One or more exclusion criteria
L1	Adimalla, N.. Controlling factors and mechanism of groundwater quality variation in semiarid region of South India: an approach of water quality index (WQI) and health risk assessment (HRA). <i>Environ Geochem Health</i> . 2019. #volume#: #pages#	One or more exclusion criteria
L1	Enriquez, J. S., Yu, M., Bouley, B. S., Xie, D., Que, E. L.. Copper(ii) complexes for cysteine detection using (19)F magnetic resonance. <i>Dalton Trans</i> . 2018. 47:15024-15030	One or more exclusion criteria
L1	Wu, Y., Yang, D., Kang, X., Ma, P., Huang, S., Zhang, Y., Li, C., Lin, J.. Core-shell structured luminescent and mesoporous beta-NaYF4:Ce3+/Tb3+@mSiO2-PEG nanospheres for anti-cancer drug delivery. <i>Dalton Transactions</i> . 2013. 42:9852-61	One or more exclusion criteria
L1	Jeong, J. H., Cho, I. H., Chun, K. A., Kong, E. J., Kwon, S. D., Kim, J. H.. Correlation Between Apparent Diffusion Coefficients and Standardized Uptake Values in Hybrid (18)F-FDG PET/MR: Preliminary Results in Rectal Cancer.	One or more exclusion criteria

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L1	Kheradpisheh, Z.,Mahvi, A. H.,Mirzaei, M.,Mokhtari, M.,Azizi, R.,Fallahzadeh, H.,Ehrampoush, M. H.. Correlation between drinking water fluoride and TSH hormone by ANNs and ANFIS. <i>Journal of Environmental Health Science & Engineering</i> . 2018. 16:11-18	One or more exclusion criteria
L1	Faraji, H.,Mohammadi, A. A.,Akbari-Adergani, B.,Vakili Saatloo, N.,Lashkarboloki, G.,Mahvi, A. H.. Correlation between Fluoride in Drinking Water and Its Levels in Breast Milk in Golestan Province, Northern Iran. <i>Iranian Journal of Public Health</i> . 2014. 43:1664-8	One or more exclusion criteria
L1	Wu, J.,Li, D.,Yang, D.,Qin, M.,Li, B.,Liu, X.,Li, M.,Li, Y.,Zhang, W.,Gao, Y.. Correlation between urinary fluoride level and i ntaking of fluoride per day in Tibetan and Kazakh population in brick-tea-borne fluorosis areas. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2015. 34:549-552	One or more exclusion criteria
L1	Ahmed, I.,Rafique, T.,Hasan, S. K.,Khan, N.,Khan, M. H.,Usmani, T. H.. Correlation of fluoride in drinking water with urine, blood plasma, and serum fluoride levels of people consuming high and low fluoride drinking water in Pakistan. <i>Fluoride</i> . 2012. 45:384-388	One or more exclusion criteria
L1	Mariño, R.,Fajardo, J.,Morgan, M.. Cost-effectiveness models for dental caries prevention programmes among Chilean schoolchildren. <i>Community Dent Health</i> . 2012. 29:302-8	One or more exclusion criteria
L1	Chansaenpak, K.,Kamkaew, A.,Weeranantapan, O.,Suttisintong, K.,Tumcharern, G.. Coumarin Probe for	One or more exclusion criteria

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L1	<p>Cai, H.,Zhu, X.,Peng, C.,Xu, W.,Li, D.,Wang, Y.,Fang, S.,Li, Y.,Hu, S.,Wan, X.. Critical factors determining fluoride concentration in tea leaves produced from Anhui province, China. <i>Ecotoxicol Environ Saf</i>. 2016. 131:14-21</p>	One or more exclusion criteria
L1	<p>Shinoda, T.,Ogawa, H.,Cornelius, F.,Toyoshima, C.. Crystal structure of the sodium-potassium pump at 2.4 Å resolution. <i>Nature</i>. 2009. 459:446-50</p>	One or more exclusion criteria
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L1	Ge, Q. D.,Xie, C.,Zhang, H.,Tan, Y.,Wan, C. W.,Wang, W. J.,Jin, T. X.. Differential Expression of miRNAs in the Hippocampi of Offspring Rats Exposed to Fluorine	One or more exclusion criteria

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L1	Wang, M.,Li, X.,He, W. Y.,Li, J. X.,Zhu, Y. Y.,Liao, Y. L.,Yang, J. Y.,Yang, X. E.. Distribution, health risk assessment, and anthropogenic sources of fluoride in farmland soils in phosphate industrial area, southwest China. <i>Environ Pollut.</i> 2019. 249:423-433	One or more exclusion criteria
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L1	Sacco, D. E.,Cleveland, R. O.,Kracht, J. M.,Dretler, S. P.. Do lithotriptors maintain their effectiveness over time?. <i>Journal of Urology</i> . 2009. 1):582	One or more exclusion criteria
L1	Clincha, C.. Does dental fluoride use have clinically significant effects on oral bacteria?. <i>Fluoride</i> . 2010. 43:205-214	One or more exclusion criteria
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L1	Torres, L.,August, A.. Does perfluorooctane sulfonic acid (PFOS) affect the mouse immune system?. <i>FASEB Journal. Conference: Experimental Biology</i> . 2018. 32:#pages#	One or more exclusion criteria
L1	Sonego, I. L.,Huber, A. C.,Mosler, H. J.. Does the implementation of hardware need software? A longitudinal study on fluoride-removal filter use in Ethiopia. <i>Environ Sci Technol</i> . 2013. 47:12661-8	One or more exclusion criteria
L1	Mohapatra, S.,Das, R. K.. Dopamine integrated B, N, S doped CQD nanoprobe for rapid and selective detection of fluoride ion. <i>Anal Chim Acta</i> . 2019. 1058:146-154	One or more exclusion criteria
L1	Cui, Y.,Zhang, B.,Ma, J.,Wang, Y.,Zhao, L.,Hou, C.,Yu,	One or more exclusion

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L1	Bhardwaj, M.,Shashi, A.. Dose effect relationship between high fluoride intake and biomarkers of lipid metabolism in endemic fluorosis. <i>Biomedicine and Preventive Nutrition</i> . 2013. 3:121-127	One or more exclusion criteria
L1	Khandare, A. L.,Validandi, V.,Gourineni, S. R.,Gopalan, V.,Nagalla, B.. Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study. <i>Environmental Monitoring and Assessment</i> . 2018. 190 (3) (no pagination):#pages#	One or more exclusion criteria
L1	Chandrajith, R.,Dissanayake, C. B.,Ariyaratna, T.,Herath, H. M.,Padmasiri, J. P.. Dose-dependent Na and Ca in fluoride-rich drinking water--another major cause of chronic renal failure in tropical arid regions. <i>Sci Total Environ</i> . 2011. 409:671-5	One or more exclusion criteria
L1	Xiong, X.,Liu, J.,He, W.,Xia, T.,He, P.,Chen, X.,Yang, K.,Wang, A.. Dose-effect relationship between drinking water fluoride levels and damage to liver and kidney functions in children. <i>Environmental Research</i> . 2007. 103:112-116	One or more exclusion criteria
L1	Xiang, Q. Y.,Zhou, M. H.,Wu, M.,Tao, R.,Chen, L. S.,Zhang, M. F.,Liang, Y. X.. Dose-respones relationship between daily total fluoride intake and prevalence of	One or more exclusion criteria

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L1	Xiang, Q.. Dose-response relationships between drinking water fluoride, bone mineral density, and serum osteocalcin. <i>Fluoride</i> . 2012. 45 (3 PART 1):210-211	One or more exclusion criteria
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. <i>Appl Radiat Isot</i> . 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). <i>Ann Occup Environ Med</i> . 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. <i>Eur J Public Health</i> . 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. <i>Cancer Causes Control</i> . 2011. 22:919-24	One or more exclusion criteria
L1	Nazemi, S.,Dehghani, M.. Drinking water fluoride and child dental caries in Khartooran, Iran. <i>Fluoride</i> . 2014. 47:85-91	One or more exclusion criteria
L1	Vitoria Minana, I.. Drinking water in infants. Is there any ideal composition?. [Spanish]. <i>Acta Pediatrica Espanola</i> . 2009. 67:255-266	One or more exclusion criteria
L1	Narsimha, A.,Sudarshan, V.. Drinking water pollution with	One or more exclusion

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L1	Frazao, P.,Peres, M. A.,Cury, J. A.. Drinking water quality and fluoride concentration. [Portuguese]. <i>Revista de Saude Publica</i> . 2011. 45:964-973	One or more exclusion criteria
L1	Beaudeau, P.,Schwartz, J.,Levin, R.. Drinking water quality and hospital admissions of elderly people for gastrointestinal illness in Eastern Massachusetts, 1998-2008. <i>Water Research</i> . 2014. 52:188-198	One or more exclusion criteria
L1	Levallois, P.,Villanueva, C. M.. Drinking water quality and human health: An editorial. <i>International Journal of Environmental Research and Public Health</i> . 2019. 16 (4) (no pagination):#pages#	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 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	One or more exclusion criteria

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L1	Liu, Z.,Radtke, M. A.,Wong, M. Q.,Lin, K. S.,Yapp, D. T.,Perrin, D. M.. Dual mode fluorescent (18)F-PET tracers: efficient modular synthesis of rhodamine-[cRGD]2-[(18)F]-organotrifluoroborate, rapid, and high yielding one-step (18)F-labeling at high specific activity, and correlated in vivo PET imaging and ex vivo fluorescence. <i>Bioconjug Chem</i> . 2014. 25:1951-62	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. <i>Chemosphere</i> . 2007. 67:1-12	One or more exclusion criteria
L1	Bobak, M., Dunn, J. R.. Editorial note: Peckham versus Newton. <i>J Epidemiol Community Health</i> . 2017. 71:317	One or more exclusion criteria
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L1	Yoshitomi, B., Nagano, I.. Effect of dietary fluoride derived from Antarctic krill (<i>Euphausia superba</i>) meal on growth of yellowtail (<i>Seriola quinqueradiata</i>). <i>Chemosphere</i> . 2012. 86:891-7	One or more exclusion criteria
L1	Saxena, S., Sahay, A., Goel, P.. Effect of fluoride exposure on the intelligence of school children in Madhya Pradesh, India. <i>Journal of Neurosciences in Rural Practice</i> . 2012. 3:144-149	One or more exclusion criteria
L1	Aghaei, M., Derakhshani, R., Raoof, M., Dehghani, M., Mahvi, A. H.. Effect of fluoride in drinking water on birth height and weight: An ecological study in Kerman Province, Zarand county, Iran. <i>Fluoride</i> . 2015. 48:160-168	One or more exclusion criteria
L1	Goudu, A. S., Naidu, M. D.. Effect of fluoride on oxidative stress and biochemical markers of bone turnover in	One or more exclusion criteria

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L1	Shashi, A.,Kumar, M.. Effect of high fluoride ingestion on serum biochemical indices in patients of skeletal fluorosis. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences</i> . 2008. 10:569-576	One or more exclusion criteria
L1	Wang, F.,Hou, T. Z.,Li, J. J.,Li, Z. Z.,Tang, C. F.. Effect of magnesium and selenium on the expression of matrix metalloproteinases-20 and kallikrein 4 in fluorosis mice. [Chinese]. <i>Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology</i> . 2016. 51:546-551	One or more exclusion criteria
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L1	Zandim, D. L.,Tschoppe, P.,Sampaio, J. E.,Kielbassa, A. M.. Effect of saliva substitutes in combination with fluorides on remineralization of subsurface dentin lesions. <i>Support Care Cancer</i> . 2011. 19:1143-9	One or more exclusion criteria
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L1	Freitas, A. S.,Fontes Cunha, I. M.,Andrade-Vieira, L. F.,Techio, V. H.. Effect of SPL (Spent Pot Liner) and its main components on root growth, mitotic activity and phosphorylation of Histone H3 in <i>Lactuca sativa</i> L. <i>Ecotoxicology & Environmental Safety</i> . 2016. 124:426-434	One or more exclusion criteria
L1	Dowling, D. P.,Miller, I. S.,Ardhaoui, M.,Gallagher, W. M.. Effect of surface wettability and topography on the adhesion of osteosarcoma cells on plasma-modified polystyrene. <i>J Biomater Appl</i> . 2011. 26:327-47	One or more exclusion criteria
L1	Salvio, L. A.,DoCarmo, V. C. F. T.,Andrade, T. P. S.,Baroudi, K.. Effect of the combined use of adhesive systems and oxalate-based and fluoride-based dentin desensitizers on bond strength. <i>Journal of Clinical and Diagnostic Research</i> . 2019. 13:ZC17-ZC21	One or more exclusion criteria
L1	Murata, S.,Izumi, T.,Ito, H.. Effect of the moisture content in	One or more exclusion

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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). <i>Journal of Biomedical Research</i> . 2011. 25:254-258	One or more exclusion criteria
L1	Antoniuzzi, 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. <i>Am J Dent</i> . 2014. 27:251-7	One or more exclusion criteria
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L1	Olley, R. C.,Moazzez, R.,Bartlett, D.. Effects of dentifrices on subsurface dentin tubule occlusion: an in situ study. <i>Int J Prosthodont</i> . 2015. 28:181-7	One or more exclusion criteria
L1	Yang, M.,Lin, H.,Jiang, R.,Zheng, G.. Effects of desensitizing toothpastes on the permeability of dentin after different brushing times: An in vitro study. <i>Am J Dent</i> . 2016. 29:345-351	One or more exclusion criteria
L1	Sushma Susik, M. S.,Ajay Prakash, P.,Madhusudhan Rao, T.. Effects of different concentrations of fluoride in oral mucosal cells in albino rats. <i>J Clin Diagn Res</i> . 2015. 9:ZF01-ZF04	One or more exclusion criteria
L1	Wang, J. Y.,Li, B. L.,Zhao, X. H.,Huang, Y. X.,Chen, J. K.,Chen, S. H.,Ou, H. H.,Chen, S. X.. Effects of drinking water defluoride in endemic fluorosis areas in Shantou city of Guangdong province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2013. 32:71-73	One or more exclusion criteria
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. E.,McNeil, D. W.,Crout, R.	One or more exclusion criteria

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L1	Ludlow, M.,Luxton, G.,Mathew, T.. Effects of fluoridation of community water supplies for people with chronic kidney disease. <i>Nephrol Dial Transplant</i> . 2007. 22:2763-7	One or more exclusion criteria
L1	Shahab, S.,Mustafa, G.,Khan, I.,Zahid, M.,Yasinzai, M.,Ameer, N.,Asghar, N.,Ullah, I.,Nadhman, A.,Ahmed, A.,Munir, I.,Mujahid, A.,Hussain, T.,Ahmad, M. N.,Ahmad, S. S.. Effects of fluoride ion toxicity on animals, plants, and soil health: A review. <i>Fluoride</i> . 2017. 50:393-408	One or more exclusion criteria
L1	Goyal, N.,Dulawat, M. S.,Dulawat, S. S.. Effects of fluoride on human health in Rajasthan. <i>Advanced Science, Engineering and Medicine</i> . 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 (<i>Bufo gargarizans</i>) embryos. <i>Environ Mol Mutagen</i> . 2018. 59:123-133	One or more exclusion criteria
L1	Levy, S. M.,Warren, J. J.,Phipps, K.,Letuchy, E.,Broffitt, B.,Eichenberger-Gilmore, J.,Burns, T. L.,Kavand, G.,Janz, K. F.,Torner, J. C.,Pauley, C. A.. Effects of life-long fluoride intake on bone measures of adolescents: a prospective	One or more exclusion criteria

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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. <i>Acta Biomaterialia.</i> 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. <i>Fluoride.</i> 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 <i>Allium cepa</i> . <i>Journal of Environmental Management.</i> 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 hypertensive rats with hyperactivity of liver-yang: A [F-18] FDG micro-PET imaging study. <i>Biomed Pharmacother.</i> 2017. 95:1838-1843	One or more exclusion criteria
L1	Ju, X.,Brennan, D.,Parker, E.,Mills, H.,Kapellas, K.,Jamieson, L.. Efficacy of an oral health literacy intervention among Indigenous Australian adults.	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. <i>Bioconjug Chem.</i> 2012. 23:1557-66	One or more exclusion criteria
L1	Otabashi, M., Vergote, T., Desfours, C.. Efficient commercial scale 18F-FES production on AllinOne (Trasis). <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.</i> 2017. 58:#pages#	One or more exclusion criteria
L1	Deraedt, Q., Masset, J., Otabashi, M., Philippart, G.. Efficient commercial scale [¹⁸ F]FES production on AllinOne (Trasis). <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2017. 60 (Supplement 1):S195	One or more exclusion criteria
L1	Chen, R., Yu, H., Jia, Z. Y., Yao, Q. L., Teng, G. J.. Efficient nano iron particle-labeling and noninvasive MR imaging of mouse bone marrow-derived endothelial progenitor cells. <i>Int J Nanomedicine.</i> 2011. 6:511-9	One or more exclusion criteria
L1	Zhang, S., He, Y., Wang, X., Li, G., Ding, R., Xu, J., Feng, M., Liu, H., Qi, C., Peng, C.. Efficient radiosynthesis and evaluation of fluorine-18 labeled benzimidazol derivatives for peripheral tumor imaging. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2009. 1):S153	One or more exclusion criteria

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L1	Wang, Z.,Guo, X.,Bai, G.,Lei, Y.,Wang, Y.,Fan, Z.,Zhang, Q.,Ding, Y.. Elevated levels of arsenic and fluoride, but not selenium, associated with endemic disease in the Chinese village of Dazhuyuan, Shaanxi Province. <i>Fluoride</i> . 2009. 42:34-38	One or more exclusion criteria
L1	Nelson, J. D.,Spencer, S. M.,Blake, C. E.,Moore, J. B.,Martin, A. B.. Elevating Oral Health Interprofessional Practice Among Pediatricians Through a Statewide Quality Improvement Learning Collaborative. <i>J Public Health Manag Pract</i> . 2018. 24:e19-e24	One or more exclusion criteria
L1	Patel, R. K.,Kumar, S.,Chawla, A. K.,Mondal, P.,Neelam,,Teychene, B.,Pandey, J. K.. Elimination of fluoride, arsenic, and nitrate from water through adsorption onto nano-adsorbent: A review. <i>Current Nanoscience</i> . 2019. 15:557-575	One or more exclusion criteria
L1	Pandey, P.,Khan, F.,Mishra, R.,Singh, S. K.. Elucidation of the potential of Moringa oleifera leaves extract as a novel alternate to the chemical coagulant in water treatment process. <i>Water Environ Res</i> . 2020. #volume#:#pages#	One or more exclusion criteria
L1	Opydo-Szymaczek, J.,Gerreth, K.,Borysewicz-Lewicka, M.,Pawlaczyk-Kamienska, T.,Torlinska-Walkowiak, N.,Sniatala, R.. Enamel defects and dental caries among children attending primary schools in Poznan, Poland.	One or more exclusion criteria

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L1	Bagh, B.. Endemic fluoride pollution in drinking water and its impact on human health and management by bio-remediation. <i>Fluoride</i> . 2012. 45 (3 PART 1):152-153	One or more exclusion criteria
L1	Brandt Jr, E. N.. Endemic fluorosis and its relation to dental caries (1938): Commentary. <i>Public Health Reports</i> . 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. <i>Fluoride</i> . 2008. 41:206-211	One or more exclusion criteria
L1	Ding, S. R.,Lu, Q.,Ding, P.,Si, W. J.,Pu, G. L.,Yang, P.. Endemic fluorosis in guide county of Qinghai province in 2008: An analysis of surveillance results. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:306-308	One or more exclusion criteria
L1	Chen, P.,Wei, S. Y.,Ding, P.,Lu, Q.,He, D. L.,Wu, H. K.,Pu, G. L.,Tan, D. F.,Zheng, J. Z.. Endemic fluorosis in Huangyuan county Qinghai province in 2009: An analysis of surveillance results. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:303-305	One or more exclusion criteria
L1	Zhang, H. T.,Lu, Z. M.,Tang, H. Y.,Zhang, X. L.,Fang, L. Y.. Endemic fluorosis in Jilin province: Analysis of surveillance data for 2006-2010. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:298-302	One or more exclusion criteria
L1	Ma, J.,Lu, S. M.,Zhang, H. P.,Du, Y. G.,Yao, G. J.,Zhang, K. J.,Li, Y.,Zhao, G. J.. Endemic fluorosis in Sanhe City of Hebei Province in 2004 and 2005: An analysis of the outcome. [Chinese]. <i>Chinese Journal of Endemiology</i> .	One or more exclusion criteria

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	2007. 26:168-169	
L1	Sharmila, C.,Subramanian, S. P.. Endemic fluorosis in vellore district, tamil nadu - a bio-geochemical approach. <i>International Journal of Pharmaceutical Sciences Review and Research</i> . 2019. 54:58-66	One or more exclusion criteria
L1	Li, J.,Wang, Z. H.,Cheng, X. T.,Jia, Q. Z.,Sang, Z. P.,Zhang, J.,Han, L. L.,Duan, H. S.,Liang, B. F.,Wang, S. X.. Endemic fluorosis prevalence in the counties of severe disease areas of Shanxi Province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:541-543	One or more exclusion criteria
L1	Yu, S. Q.,Wang, W. L.,Jia, J. X.,Chen, X. Y.,Shao, J. Y.,Bai, S. Y.,Wang, W. H.. Endemic fluorosis surveillance in Qinan County of Gansu Province from 2004 to 2007: An outcome analysis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2009. 28:545-547	One or more exclusion criteria
L1	Wang, J. H.,Zheng, Z. X.,Liu, W.,Liu, Y.,Gao, R.,Li, Z. R.,Zhao, W. G.,Wang, S. Q.,Liu, W. Y.. Endemic fluorosis: Prevalence and prevention in Liaoning Province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2008. 27:663-667	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 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. <i>PLoS One</i> . 2011. 6:e21085	One or more exclusion criteria

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L1	Chen, Y.,Ginga, N. J.,LePage, W. S.,Kazyak, E.,Gayle, A. J.,Wang, J.,Rodriguez, R. E.,Thouless, M. D.,Dasgupta, N. P.. Enhanced Interfacial Toughness of Thermoplastic-Epoxy Interfaces Using ALD Surface Treatments. <i>ACS applied materials & interfaces</i> . 2019. 11:43573-43580	One or more exclusion criteria
L1	Viswanathan, N.,Meenakshi, S.. Enriched fluoride sorption using alumina/chitosan composite. <i>Journal of Hazardous Materials</i> . 2010. 178:226-232	One or more exclusion criteria
L1	Lash, L. H.. Environmental and Genetic Factors Influencing Kidney Toxicity. <i>Semin Nephrol</i> . 2019. 39:132-140	One or more exclusion criteria
L1	Tsai, W. T.. Environmental and health risk analysis of nitrogen trifluoride (NF(3)), a toxic and potent greenhouse gas. <i>J Hazard Mater</i> . 2008. 159:257-63	One or more exclusion criteria
L1	Sengupta, P.. Environmental and occupational exposure of metals and their role in male reproductive functions. <i>Drug and Chemical Toxicology</i> . 2013. 36:353-368	One or more exclusion criteria
L1	Mondal, P.,Chattopadhyay, A.. Environmental exposure of arsenic and fluoride and their combined toxicity: A recent update. <i>Journal of Applied Toxicology</i> .. 2019. #volume#:#pages#	One or more exclusion criteria
L1	Molina-Frechero, N.,Nevarez-Rascón, M.,Tremillo-Maldonado, O.,Vergara-Onofre, M.,Gutiérrez-Tolentino, R.,Gaona, E.,Castañeda, E.,Jarquin-Yañez, L.,Bologna-Molina, R.. Environmental Exposure of Arsenic in Groundwater Associated to Carcinogenic Risk in Underweight Children Exposed to Fluorides. <i>Int J Environ Res Public Health</i> . 2020. 17:#pages#	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-Maldonado, I. N.,Sabbisetti, V. S.,Bonventre, J. V.,Vaidya, V. S.. Environmental exposure to arsenic and chromium in children is associated with kidney injury molecule-1. <i>Toxicology Letters</i> . 2016. 259 (Supplement 1):S158	One or more exclusion criteria
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.. Environmental exposure to arsenic and chromium in children is associated with kidney injury molecule-1. <i>Environmental Research</i> . 2016. 150:653-662	One or more exclusion criteria
L1	Tsai, W. T.. Environmental hazards and health risk of common liquid perfluoro-n-alkanes, potent greenhouse gases. <i>Environ Int</i> . 2009. 35:418-24	One or more exclusion criteria
L1	Etzel, R. A.. Environmental hazards that matter for children's health. <i>Hong Kong Journal of Paediatrics</i> . 2015. 20:86-94	One or more exclusion criteria
L1	Patil, R. R.. Environmental health impact assessment of national aluminum company, Orissa. <i>Indian Journal of Occupational and Environmental Medicine</i> . 2011. 15:73-75	One or more exclusion criteria
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. <i>J Toxicol Environ Health A</i> . 2012. 75:1437-50	One or more exclusion criteria
L1	Malone Rubright, S. L.,Pearce, L. L.,Peterson, J..	One or more exclusion

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	Environmental toxicology of hydrogen sulfide. <i>Nitric Oxide - criteria Biology and Chemistry</i> . 2017. 71:1-13	
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). <i>Org Biomol Chem</i> . 2019. 17:1480-1486	One or more exclusion criteria
L1	Thompson, S.,Fleming, I. N.,O'Hagan, D.. Enzymatic transhalogenation of dendritic RGD peptide constructs with the fluorinase. <i>Org Biomol Chem</i> . 2016. 14:3120-9	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2012. 31:566-570	One or more exclusion criteria
L1	Yun, Z. J.,Bian, J. C.,Chen, P. Z.,Pang, X. G.,Qin, Q. L.,Zhao, L. J.,Wang, Y. T.. Epidemiological investigation of endemic fluorosis along the Yellow River basin of Shandong Province. [Chinese]. <i>Chinese Journal of</i>	One or more exclusion criteria

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	<i>Endemiology</i> . 2008. 27:174-176	
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2009. 28:75-77	One or more exclusion criteria
L1	Yousefi, M.,Mohammadi, A. A.,Yaseri, M.,Mahvi, A. H.. Epidemiology of drinking water fluoride and its contribution to fertility, infertility, and abortion: An ecological study in west Azerbaijan province, poldasht county, Iran. <i>Fluoride</i> . 2017. 50:343-353	One or more exclusion criteria
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. <i>Ethiopian Medical Journal</i> . 2012. 50:307-313	One or more exclusion criteria
L1	Melaku, 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. <i>Ethiop Med J</i> . 2012. 50:307-13	One or more exclusion criteria
L1	Kulkarni, P.,Anand, A.,Bansal, A.,Jain, A.,Tiwari, U.,Agrawal, S.. Erosive effects of pediatric liquid medicinal syrups on primary enamel: An in vitro comparative study. <i>Indian J Dent</i> . 2016. 7:131-133	One or more exclusion criteria

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L1	Vieira, A. M.,Neto, F.,Carvalho, P.,Manso, A. C.. Erosive potential of medication on human enamel and posterior remineralization capacity. <i>Annals of Medicine</i> . 2019. 51 (Supplement 1):S107-S109	One or more exclusion criteria
L1	Wimalawansa, S. J.. Escalating chronic kidney diseases of multi-factorial origin (CKD-mfo) in Sri Lanka: causes, solutions, and recommendations-update and responses. <i>Environmental Health and Preventive Medicine</i> . 2015. 20:152-157	One or more exclusion criteria
L1	Misra, S. K.. Essentials of specifications for activated alumina in defluoridation technology. <i>J Environ Sci Eng</i> . 2006. 48:231-40	One or more exclusion criteria
L1	Näsman, P.,Ekstrand, J.,Granath, F.,Ekbom, A.,Fored, C. M.. Estimated drinking water fluoride exposure and risk of hip fracture: a cohort study. <i>J Dent Res</i> . 2013. 92:1029-34	One or more exclusion criteria
L1	Awofeso, N.. Ethics of artificial water fluoridation in Australia. <i>Public Health Ethics</i> . 2012. 5:161-172	One or more exclusion criteria
L1	Joshua, A. D.,NethajiMariappan, V. E.,Anne, B. M.,Vadivel, N.. Evaluating fluoride contamination in ground water of Dharmapuri district in Tamilnadu. <i>Journal of Chemical and Pharmaceutical Sciences</i> . 2015. 8:18-24	One or more exclusion criteria
L1	Loccisano, A. E.,Campbell, J. L., Jr.,Andersen, M. E.,Clewell, H. J., 3rd. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. <i>Regul Toxicol Pharmacol</i> . 2011. 59:157-75	One or more exclusion criteria
L1	Pollo, F. E.,Grenat, P. R.,Salinas, Z. A.,Otero, M. A.,Salas, N. E.,Martino, A. L.. Evaluation in situ of genotoxicity and	One or more exclusion criteria

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	stress in South American common toad <i>Rhinella arenarum</i> in environments related to fluorite mine. <i>Environ Sci Pollut Res Int.</i> 2017. 24:18179-18187	criteria
L1	Fekrazad, R.,Ebrahimpour, L.. Evaluation of acquired acid resistance of enamel surrounding orthodontic brackets irradiated by laser and fluoride application. <i>Lasers in Medical Science.</i> 2014. 29:1793-1798	One or more exclusion criteria
L1	Bhardwaj, M.,Aggarwal, S.. Evaluation of biochemical interaction and correlation between high fluoride ingestion and protein metabolism. <i>Biomedicine and Preventive Nutrition.</i> 2013. 3:129-137	One or more exclusion criteria
L1	Tomlinson, R.,Shoghi, K.,Silva, M.. Evaluation of blood flow and skeletal kinetics during loading induced osteogenesis using pet imaging. <i>Journal of Bone and Mineral Research.</i> 2010. 1):S70-S71	One or more exclusion criteria
L1	Moazeni, M.,Atefi, M.,Ebrahimi, A.,Razmjoo, P.,Vahid Dastjerdi, M.. Evaluation of chemical and microbiological quality in 21 brands of iranian bottled drinking waters in 2012: A comparison study on label and real contents. <i>Journal of Environmental and Public Health.</i> 2013. 2013 (no pagination):#pages#	One or more exclusion criteria
L1	Tran, M. T.,Shah, S. R.,Kim, K.,Trinidad, P.,Pandey, S.,Karmur, A.,Patel, R.,Kant, R.,Mukherjee, J.. Evaluation of dopamine receptor agonists, 18F-5-OH-FPPAT, 18F-5-OH-FHXPAT and 18F-7-OH-FHXPAT. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2009. 1):S345	One or more exclusion criteria
L1	Sarmah, S. P.,Chutia, J.. Evaluation of drinking water quality in Bihpuria area of Lakhimpur District, Assam, India.	One or more exclusion criteria

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	<i>Research Journal of Pharmaceutical, Biological and Chemical Sciences</i> . 2012. 3:1030-1036	
L1	Ramesh, M. V., Naveenkumar, P. G., Prashant, G. M., Sakeenabi, B., Allamaprabhu, Vijetha, K.. Evaluation of effect of brushite-calcite and two indigenous herbs in removal of fluoride from water. <i>Journal of Clinical and Diagnostic Research</i> . 2016. 10:ZC83-ZC85	One or more exclusion criteria
L1	Rocha, R. A., Calatayud, M., Devesa, V., Velez, D.. Evaluation of exposure to fluoride in child population of North Argentina. <i>Environmental Science & Pollution Research</i> . 2017. 24:22040-22047	One or more exclusion criteria
L1	Stramare, R., Raffener, B., Ciprian, L., Scagliori, E., Coran, A., Perissinotto, E., Fiocco, U., Beltrame, V., Rubaltelli, L.. Evaluation of finger joint synovial vascularity in patients with rheumatoid arthritis using contrast-enhanced ultrasound with water immersion and a stabilized probe. <i>J Clin Ultrasound</i> . 2012. 40:147-54	One or more exclusion criteria
L1	Bengharez, Z., Farch, S., Bendahmane, M., Merine, H., Benyahia, M.. Evaluation of fluoride bottled water and its incidence in fluoride endemic and non endemic areas. <i>e-SPEN Journal</i> . 2012. 7:e41-e45	One or more exclusion criteria
L1	Abouleish, M. Y.. Evaluation of fluoride levels in bottled water and their contribution to health and teeth problems in the United Arab Emirates. <i>Saudi Dent J</i> . 2016. 28:194-202	One or more exclusion criteria
L1	Singh, G., Rishi, M. S., Herojeet, R., Kaur, L., Sharma, K.. Evaluation of groundwater quality and human health risks from fluoride and nitrate in semi-arid region of northern India. <i>Environmental Geochemistry & Health</i> . 2019. 05:05	One or more exclusion criteria

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L1	Elumalai, V.,Nwabisa, D. P.,Rajmohan, N.. Evaluation of high fluoride contaminated fractured rock aquifer in South Africa - Geochemical and chemometric approaches. <i>Chemosphere</i> . 2019. 235:1-11	One or more exclusion criteria
L1	Pant, H. H.,Rao, M. V.. Evaluation of in vitro anti-genotoxic potential of melatonin against arsenic and fluoride in human blood cultures. <i>Ecotoxicol Environ Saf</i> . 2010. 73:1333-7	One or more exclusion criteria
L1	Samuel, S. R.,Khatri, S. G.,Acharya, S.,Patil, S. T.. Evaluation of instant desensitization after a single topical application over 30 days: a randomized trial. <i>Aust Dent J</i> . 2015. 60:336-42	One or more exclusion criteria
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. <i>Toxicol Appl Pharmacol</i> . 2018. 352:97-106	One or more exclusion criteria
L1	Jimenez-Cordova, M. I.,Gonzalez-Horta, M. C.,Aguilar-Madrid, G.,Barrera-Hernandez, A.,Sanchez-Pena, L. C.,Barbier, O. C.,Del Razo, L. M.. Evaluation of KIM-1, Cystatin-C and glomerular filtration rate in schoolchildren exposed to inorganic fluoride. <i>Toxicology Letters</i> . 2016. 259 (Supplement 1):S131	One or more exclusion criteria
L1	Brooks, A.,Jackson, I.,Scott, P.. Evaluation of metal-protein aggregate radioligand [¹⁸ F]FL2-b by small animal PET imaging and autoradiography in alzheimer's	One or more exclusion criteria

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	disease, amyotrophic lateral sclerosis, and lewy body dementia. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.</i> 2017. 58:#pages#	
L1	J, M.,Sinha, S.,Ghosh, M.,Mukherjee, A.. Evaluation of multi-endpoint assay to detect genotoxicity and oxidative stress in mice exposed to sodium fluoride. <i>Mutat Res.</i> 2013. 751:59-65	One or more exclusion criteria
L1	Adekiitan, M. E.,Imana, G. E.,Adedeji, O. O.. Evaluation of new glucometers (Easy Touch GC) for bedside use. <i>Clinical Chemistry.</i> 2014. 1):S214	One or more exclusion criteria
L1	Karunanidhi, D.,Aravinthasamy, P.,Roy, P. D.,Praveenkumar, R. M.,Prasanth, K.,Selvapraveen, S.,Thowbeekrahman, A.,Subramani, T.,Srinivasamoorthy, K.. Evaluation of non-carcinogenic risks due to fluoride and nitrate contaminations in a groundwater of an urban part (Coimbatore region) of south India. <i>Environ Monit Assess.</i> 2020. 192:102	One or more exclusion criteria
L1	Wang, Y.,Yu, R.,Zhu, G.. Evaluation of Physicochemical Characteristics in Drinking Water Sources Emphasized on Fluoride: A Case Study of Yancheng, China. <i>Int J Environ Res Public Health.</i> 2019. 16:#pages#	One or more exclusion criteria
L1	Maga, K.,Lamba, M.. Evaluation of respiratory gating of roi definition on the accuracy of suv in f18-FDG pet imaging. <i>International Journal of Radiation Oncology Biology Physics.</i> 2010. 1):S814	One or more exclusion criteria
L1	Ortega-Romero, M. S.,Hernandez Sanchez, A. M.,Medeiros-Domingo, M.,Barbier, O.. Evaluation of risk	One or more exclusion criteria

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	factors for renal disease in a pediatric Mexican meztizo population from Apizaco in Tlaxcala Mexico. <i>Toxicology Letters</i> . 2016. 259 (Supplement 1):S242	
L1	Yur, F.,Mert, N.,Dede, S.,Deger, Y.,Ertekin, A.,Mert, H.,Yasar, S.,Dogan, I.,Isik, A.. Evaluation of serum lipoprotein and tissue antioxidant levels in sheep with fluorosis. <i>Fluoride</i> . 2013. 46:90-96	One or more exclusion criteria
L1	Magnusson, R.,Rittfeldt, L.,. Evaluation of sorbent materials for the sampling and analysis of phosphine, sulfuryl fluoride and methyl bromide in air. <i>J Chromatogr A</i> . 2015. 1375:17-26	One or more exclusion criteria
L1	Whittaker, P.,Clarke, J. J.,San, R. H.,Begley, T. H.,Dunkel, V. C.. Evaluation of the butter flavoring chemical diacetyl and a fluorochemical paper additive for mutagenicity and toxicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. <i>Food Chem Toxicol</i> . 2008. 46:2928-33	One or more exclusion criteria
L1	Iskandarova, S.,Khasanova, M.,Fayzieva, M.,Sattarova, Z.,Mirdadaeva, D.. Evaluation of the content of microelements in the soil under the conditions of Uzbekistan. <i>International Journal of Pharmaceutical Research</i> . 2020. 12:787-791	One or more exclusion criteria
L1	Sarkar, M.,Manna, S.,Pramanick, P. P.. Evaluation of the efficiency of fly ash from thermal power plant in controlling aquatic pollution. <i>Journal of the Indian Chemical Society</i> . 2008. 85:1130-1133	One or more exclusion criteria
L1	Mori, M. M.,Airaksinen, A. J.,Hirvonen, J. T.,Santos, H. A.,Caramella, C. M.. Evaluation of the physicochemical and	One or more exclusion criteria

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	biopharmaceutical properties of fluoro-indomethacin. <i>Curr Drug Metab.</i> 2013. 14:80-9	
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 micro-CT with optimization of the scan protocol. <i>Contrast Media Mol Imaging.</i> 2010. 5:201-7	One or more exclusion criteria
L1	Jimenez-Cordova, M. I.,Gonzalez-Horta, C.,Ayllon-Vergara, J. C.,Arreola-Mendoza, L.,Aguilar-Madrid, G.,Villareal-Vega, E. E.,Barrera-Hernandez, A.,Barbier, O. C.,Del Razo, L. M.. Evaluation of vascular and kidney injury biomarkers in Mexican children exposed to inorganic fluoride. <i>Environmental Research.</i> 2019. 169:220-228	One or more exclusion criteria
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. <i>American Journal of Physical Anthropology.</i> 2014. 58):193	One or more exclusion criteria
L1	Nelson, E. A.,Halling, C. L.,Buikstra, J. E.. Evidence of Skeletal Fluorosis at the Ray Site, Illinois, USA: a pathological assessment and discussion of environmental factors. <i>Int J Paleopathol.</i> 2019. 26:48-60	One or more exclusion criteria
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. <i>Applied Psychology. Health and Well-being.</i> 2014. 6:96-118	One or more exclusion criteria
L1	Chakraborti, D.,Das, B.,Murrill, M. T.. Examining India's	One or more exclusion

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	groundwater quality management. <i>Environmental Science and Technology</i> . 2011. 45:27-33	criteria
L1	Tomar, A.,Singh, V. P.,Chauhan, D. S.,Mishra, S.,Joshi, D. K.,Kumar, S.,Tripathi, S.,Tomar, S.. Excessive fluoride exposure delineating changes in different vitamin levels and oxidative burden in school children in the eastern region of Rajasthan, India. <i>Fluoride</i> . 2012. 45 (3 PART 1):206-207	One or more exclusion criteria
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. <i>Archives of Disease in Childhood</i> . 2012. 2):A294	One or more exclusion criteria
L1	Liu, L. Z.,Wang, L. H.,Xu, C. B.,Yu, G. Q.,Fu, S. B.,Liu, Y. Q.,Shi, Y. X.,Song, L.,Wu, Y.,Yu, J.,Gao, Y. H.,Wan, G. M.,Sun, D. J.. Experimental study on the 24-hour metabolism of brick-tea fluoride in rats at the altitude of 3 290 meters above sea level. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:135-138	One or more exclusion criteria
L1	Zhou, D.,Chu, W.,Katzenellenbogen, J.. Exploration of alcohol-enhanced Cu-mediated radiofluorination towards practical labeling. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI</i> . 2018. 59:#pages#	One or more exclusion criteria
L1	Mukherjee, I.,Singh, U. K.,Patra, P. K.. Exploring a multi-exposure-pathway approach to assess human health risk associated with groundwater fluoride exposure in the semi-arid region of east India. <i>Chemosphere</i> . 2019. 233:164-173	One or more exclusion criteria
L1	Zhou, D.,Kim, S. H.,Carroll, V.,Dence, C. S.,Mach, R.	One or more exclusion

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	H.,Katzenellenbogen, J. A.. Exploring F-18 labeling of diaryodonium salts: From model reactions to F-18 radiosynthesis of a peroxisome proliferator-activated receptor-gamma (PPAR- gamma) ligand. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2013. 1):S164	criteria
L1	Malin, A. J.,Till, C.. Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. <i>Environ Health</i> . 2015. 14:17	One or more exclusion criteria
L1	Susheela, A. K.,Mondal, N. K.,Singh, A.. Exposure to fluoride in smelter workers in a primary aluminum industry in India. <i>Int J Occup Environ Med</i> . 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]. <i>Chinese Journal of Tissue Engineering Research</i> . 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. <i>Cell and Tissue Research</i> . 2006. 324:279-289	One or more exclusion criteria
L1	Schwartz, G. G.. Eye cancer incidence in U.S. states and access to fluoridated water. <i>Cancer Epidemiol Biomarkers Prev</i> . 2014. 23:1707-11	One or more exclusion criteria
L1	Jing, C.,Cui, J.,Huang, Y.,Li, A.. Fabrication, characterization, and application of a composite adsorbent	One or more exclusion criteria

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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. <i>International Journal of Environment and Pollution.</i> 2012. 49:55-61	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. <i>Sci Total Environ</i> . 2018. 635:203-215	One or more exclusion criteria
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L1	Choong, C. E.,Wong, K. T.,Jang, S. B.,Nah, I. W.,Choi, J.,Ibrahim, S.,Yoon, Y.,Jang, M.. Fluoride removal by palm shell waste based powdered activated carbon vs.	One or more exclusion criteria

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L1	Ni, J.,Zhong, Z.,Zhang, W.,Liu, B.,Shu, R.,Li, Y.. Fluoride resistance in fibroblasts is conferred via reduced susceptibility to oxidative stress and apoptosis. <i>FEBS Open Bio</i> .. 2020. #volume#:#pages#	One or more exclusion criteria
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L1	Abell, S.. Fluoride supplementation. <i>Clinical Pediatrics</i> . 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 chewing gum) in pregnant women for preventing dental caries in the primary teeth of	One or more exclusion criteria

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L1	Choubisa, S. L.. Fluoride toxicosis in immature herbivorous domestic animals living in low fluoride water endemic areas of Rajasthan, India: An observational survey. <i>Fluoride</i> . 2013. 46:19-24	One or more exclusion criteria
L1	Clark, M. B.,Slayton, R. L.. Fluoride use in caries prevention in the primary care setting. <i>Pediatrics</i> . 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. <i>International Journal of ChemTech Research</i> . 2013. 5:2614-2622	One or more exclusion criteria
L1	Spittle, B.. Fluoride, IQ, emotion, and children's school performance. <i>Fluoride</i> . 2018. 51:98-101	One or more exclusion criteria
L1	Quadri, J. A.,Sarwar, S.,Sinha, A.,Kalaivani, M.,Dinda, A. K.,Bagga, A.,Roy, T. S.,Das, T. K.,Shariff, A.. Fluoride-associated ultrastructural changes and apoptosis in human renal tubule: a pilot study. <i>Hum Exp Toxicol</i> . 2018. 37:1199-1206	One or more exclusion criteria
L1	Iafisco, M.,Degli Esposti, L.,Ramirez-Rodriguez, G. B.,Carella, F.,Gomez-Morales, J.,Ionescu, A. C.,Brambilla, E.,Tampieri, A.,Delgado-Lopez, J. M.. Fluoride-doped amorphous calcium phosphate nanoparticles as a	One or more exclusion criteria

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L1	Horst, J. A.,Tanzer, J. M.,Milgrom, P. M.. Fluorides and Other Preventive Strategies for Tooth Decay. <i>Dental Clinics of North America</i> . 2018. 62:207-234	One or more exclusion criteria
L1	Shailaja, K.,Johnson, M. E. C.. Fluorides in groundwater and its impact on health. <i>Journal of Environmental Biology</i> . 2007. 28:331-332	One or more exclusion criteria
L1	Molchanov, A.,Gust, R.. Fluorinated [1,2-diarylethylenediamine]platinum(II) complexes: differences between in vivo and in vitro cytotoxicity. <i>Journal of Cancer Research and Clinical Oncology</i> . 2012. 1):105-106	One or more exclusion criteria
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L1	Fedorova, O., Orlovskaya, V., Stepanova, M., Krasikova, R.. Fluorination efficiency and enantiomeric purity in the synthesis of O-(2-[¹⁸ F]fluoroethyl)-L-tyrosine: the role of the solvent and PTC catalyst. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2011. 1):S498	One or more exclusion criteria
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L1	Kuhnast, B.,Boisgard, R.,Hinnen, F.,Hecht, M.,Dinklerborg, L.,Friebe, M.,Tavitian, B.,Dolle, F.. Fluorine-18 labeling and evaluation in rats and tumor-bearing mice of the Tenascin-C-binding aptamer TTA-01 using [18f]FPyME. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2009. 1):S41	One or more exclusion criteria
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L1	Otabashi, M., Vergote, T., Desfours, C.. Fully automated 18F-FAZA production on AllInOne (Trasis) at commercial scale. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.</i> 2017. 58:#pages#	One or more exclusion criteria
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L1	Devalankar, D., McConathy, J.. Fully automated radiosyntheses of the ¹⁸ F-labeled amino acids MeFAMP and AFETP for oncologic imaging. <i>Journal of Nuclear Medicine. Conference.</i> 2019. 60:#pages#	One or more exclusion criteria

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L1	Nandy, S.,Chakarborthy, A.,Pawar, Y.,Ghosh, S.,Chaudhary, P. R.,Rajan, M. G. R.. Fully automated radiosynthesis of novel [18F]fluoroethylated Plumbagin derivative and its feasibility study as tumour imaging agent. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2013. 1):S396	One or more exclusion criteria
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L1	Tripathi, N.,Bajpai, S.,Tripathia, M.. Genotoxic alterations induced by fluoride in Asian catfish, <i>Clarias batrachus</i> (Linn.). <i>Fluoride.</i> 2009. 42:292-296	One or more exclusion criteria
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L1	Guidotti, T. L.,Gitterman, B. A.. Global Pediatric Environmental Health. <i>Pediatric Clinics of North America</i> . 2007. 54:335-350	One or more exclusion criteria
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L1	Stephenson, J., Sabic, H., Huber, R., Renshaw, P.. Halides in drinking water are inversely correlated with suicide rates. <i>Biological Psychiatry</i> . 2017. 81 (10 Supplement 1):S332	One or more exclusion criteria
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L1	Nayak, B., Roy, M. M., Das, B., Pal, A., Sengupta, M. K., Prasad De, S., Chakraborti, D.. Health effects of groundwater fluoride contamination. <i>Clinical Toxicology</i> . 2009. 47:292-295	One or more exclusion criteria
L1	Meghe, A. D., Quazi, Z.. Health effects of high fluoride in groundwater in parts of two districts in Central India. <i>Fluoride</i> . 2012. 45 (3 PART 1):188-189	One or more exclusion criteria
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L1	Riley, M.,Locke, A. B.,Skye, E. P.. Health maintenance in school-aged children: Part I. History, physical examination, screening, and immunizations. <i>American Family Physician</i> . 2011. 83:683-688	One or more exclusion criteria
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L1	Gao, H. J.,Jin, Y. Q.,Wei, J. L.. Health risk assessment of fluoride in drinking water from Anhui Province in China. <i>Environ Monit Assess</i> . 2013. 185:3687-95	One or more exclusion criteria
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L1	Arya, S., Subramani, T., Vennila, G., Karunanidhi, D.. Health risks associated with fluoride intake from rural drinking water supply and inverse mass balance modeling to decipher hydrogeochemical processes in Vattamalaikarai River basin, South India. <i>Environmental Geochemistry & Health</i> . 2019. 18:18	One or more exclusion criteria
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L1	Greenwood, H.. High throughput PET/CT imaging using a multiple mouse imaging system. <i>Molecular Imaging and Biology</i> . 2017. 19 (1 Supplement 1):S540	One or more exclusion criteria
L1	Subba Rao, N.. High-fluoride groundwater. <i>Environmental Monitoring and Assessment</i> . 2011. 176:637-645	One or more exclusion criteria
L1	Burnazi, E.,Carlin, S.,Lyashchenko, S.,Staton, K.,Brown, A.,Hicks, S.,Veach, D.,Lewis, J. S.. High-yield manual synthesis of 16beta-[¹⁸ F]-fluoro-5alpha-dihydrotestosterone ([¹⁸ F]FDHT) using reverse-phase HPLC purification. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2017. 60 (Supplement 1):S427-S428	One or more exclusion criteria
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L1	Moon, B. S.,Park, J. H.,Lee, H. J.,Kil, H. S.,Chi, D. Y.,Lee, B. C.,Kim, Y. K.,Kim, S. E.. Highly efficient production of	One or more exclusion criteria

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L1	<p>Krewski, D.,Yokel, R. A.,Nieboer, E.,Borchelt, D.,Cohen, J.,Harry, J.,Kacew, S.,Lindsay, J.,Mahfouz, A. M.,Rondeau,</p>	One or more exclusion criteria

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L1	Yadav, K. K.,Kumar, V.,Gupta, N.,Kumar, S.,Rezania, S.,Singh, N.. Human health risk assessment: Study of a population exposed to fluoride through groundwater of Agra city, India. <i>Regul Toxicol Pharmacol</i> . 2019. 106:68-80	One or more exclusion criteria
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L1	Aullon Alcaine, A.,Schulz, C.,Bundschuh, J.,Jacks, G.,Thunvik, R.,Gustafsson, J. P.,Morth, C. M.,Sracek, O.,Ahmad, A.,Bhattacharya, P.. Hydrogeochemical controls on the mobility of arsenic, fluoride and other geogenic co-contaminants in the shallow aquifers of northeastern La Pampa Province in Argentina. <i>Science of the Total Environment</i> . 2020. 715 (no pagination):#pages#	One or more exclusion criteria
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L1	Varol, E.,Akçay, S.,Ersoy, I. H.,Koroglu, B. K.,Varol, S.. Impact of chronic fluorosis on left ventricular diastolic and global functions. <i>Science of the Total Environment.</i> 2010. 408:2295-2298	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. <i>Environ Monit Assess.</i> 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. <i>Biomedicine (India).</i> 2018. 38:190-194	One or more exclusion criteria

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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]. <i>Medecine Tropicale</i> . 2011. 71:281-285	One or more exclusion criteria
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L1	Hariri, M.,Mirvaghefi, A.,Farahmand, H.,Taghavi, L.,Shahabinia, A. R.. In situ assessment of Karaj River genotoxic impact with the alkaline comet assay and micronucleus test, on feral brown trout (<i>Salmo trutta fario</i>). <i>Environ Toxicol Pharmacol</i> . 2018. 58:59-69	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 [¹⁸ F]FPA as a fatty acid synthasetargeting imaging agent for breast cancer and its in vivo whole-body biodistribution in normal	One or more exclusion criteria

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L1	Galal, A. A. A.,Reda, R. M.,Abdel-Rahman Mohamed, A.. Influences of <i>Chlorella vulgaris</i> dietary supplementation on growth performance, hematology, immune response and disease resistance in <i>Oreochromis niloticus</i> exposed to sub-lethal concentrations of penoxsulam herbicide. <i>Fish Shellfish Immunol</i> . 2018. 77:445-456	One or more exclusion criteria
L1	Dimachkie, P.,Peicher, K.,Maalouf, N. M.. Inhalation of air dust cleaner causing skeletal fluorosis. <i>Endocrine Reviews</i> . Conference: 99th Annual Meeting of the Endocrine Society, ENDO. 2017. 38:#pages#	One or more exclusion criteria
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L1	Aswar, S. A., Yeul, V. S., Bhagat, P. R.. Integration of ground water quality: Identifying potential hazards in Yavatmal district, India. <i>Journal of Chemical and Pharmaceutical Research.</i> 2015. 7:512-517	One or more exclusion criteria
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. <i>Toxicol Rep.</i> 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. <i>Fluoride.</i> 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]. <i>Chinese Journal of</i>	One or more exclusion criteria

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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. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2011. 1):S132	One or more exclusion criteria
L1	Wu, J. Q.,Peng, J. W.,Li, T. L.,Wu, H. Y.,Li, B. L.,Miao, L. J.. Investigating the current water-related endemic fluorosis in Shaoguan City of Guangdong Province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:535-536	One or more exclusion criteria
L1	Liu, X. L.,Bai, G. L.,Fan, Z. X.,Li, Y.,Li, X. Q.,Li, P. A.,Bai, A. M.. Investigation and analysis on endemic fluorosis associated with drinking water in Shaanxi in 2008. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:171-175	One or more exclusion criteria
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. <i>Biomedical Research (India)</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2009. 28:633-636	One or more exclusion criteria
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L1	Zhu, C. S.,Chen, Y. F.. Investigation of drinking water flouride and fluorosis in Shaanxi province from 2005 to 2007. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2009. 28:181-183	One or more exclusion criteria
L1	Sun, D. Y.,Qi, Z. M.,Ji, F. Y.,Zhang, F. X.,Liu, C. Z.,Ma, Y.. Investigation of fluoride level in drinking water and state of endemic fluorosis in Yan'an city. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:436-439	One or more exclusion criteria
L1	Karimzade, S.,Aghaei, M.,Mahvi, A. H.. Investigation of intelligence quotient in 9-12-year-old children exposed to high- and low-drinking water fluoride in West Azerbaijan Province, Iran. <i>Fluoride</i> . 2014. 47:9-14	One or more exclusion criteria
L1	Fu, S. X.,Yang, F. L.,Kang, J. S.,Ma, J.,Qiao, Y. P.,Yao, Q. L.. Investigation of status in coal-burning fluorosis areas in Luoyang city of Henan in 2006. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:190-192	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2008. 27:25-29	One or more exclusion criteria

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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]. <i>Chinese Journal of Endemiology</i> . 2007. 26:699-701	One or more exclusion criteria
L1	Yu, S. Q.,Shao, J. Y.,Liao, Y. J.,Wang, W. L.,Bai, S. Y.,Ren, Y. G.,Jia, J. X.. Investigation on status of endemic fluorosis control in Gansu province in 2006. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:179-181	One or more exclusion criteria
L1	Hou, C. C.,Han, S. Q.,Liu, Z. H.,Liu, H. L.. Investigation on the prevalent condition of adult osteofluorosis in the endemic fluorosis areas of Tianjin in 2008. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:322-324	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Journal of Clinical and Analytical Medicine</i> . 2010. 1:15-17	One or more exclusion criteria

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L1	Jentzen, W.,Weise, R.,Kupferschläger, J.,Freudenberg, L.,Brandau, W.,Bares, R.,Burchert, W.,Bockisch, A.. Iodine-124 PET dosimetry in differentiated thyroid cancer: recovery coefficient in 2D and 3D modes for PET(/CT) systems. <i>Eur J Nucl Med Mol Imaging</i> . 2008. 35:611-23	One or more exclusion criteria
L1	Burnazi, E.,Carlin, S.,Lyashchenko, S.,Rotstein, B. H.,Vasdev, N.,Lewis, J. S.. Iodonium ylide-mediated radiofluorination of [¹⁸ F]MFBG and novel formulation with cation exchange solid-phase extraction. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2017. 60 (Supplement 1):S490-S491	One or more exclusion criteria
L1	Blakey, K.,Feltbower, R. G.,Parslow, R. C.,James, P. W.,Gómez Pozo, B.,Stiller, C.,Vincent, T. J.,Norman, P.,McKinney, P. A.,Murphy, M. F.,Craft, A. W.,McNally, R. J.. Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. <i>Int J Epidemiol</i> . 2014. 43:224-34	One or more exclusion criteria
L1	Zachariassen, K. E.,Flaten, T. P.. Is fluoride-induced hyperthyroidism a cause of psychosis among East African immigrants to Scandinavia?. <i>Med Hypotheses</i> . 2009. 72:501-3	One or more exclusion criteria
L1	Gupta, S. K.,Gupta, R. C.,Gupta, A. B.. Is there a need of extra fluoride in children?. <i>Indian Pediatr</i> . 2009. 46:755-9	One or more exclusion criteria
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L1	Napolitano, R.,De Matteis, S.,Carloni, S.,Simonetti, G.,Musuraca, G.,Lucchesi, A.,Calistri, D.,Cuneo, A.,Menon, K.,Martinelli, G.. Kevetrin: Preclinical study of a new compound in acute myeloid leukemia. <i>Haematologica</i> . 2017. 102 (Supplement 2):371	One or more exclusion criteria
L1	Cox, C. D.,Breslin, M. J.,Whitman, D. B.,Coleman, P. J.,Garbaccio, R. M.,Fralely, 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. <i>Bioorg Med Chem Lett</i> . 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. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI</i> . 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 Medical and Dental Providers in the State of Hawai'i. <i>Hawaii J Med Public Health</i> . 2018. 77:275-282	One or more exclusion criteria
L1	Bottenberg, P.,Melckebeke, L. V.,Louckx, F.,Vandenplas, Y.. Knowledge of Flemish paediatricians about children's	One or more exclusion criteria

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L1	Pruss-Ustun, A.,Vickers, C.,Haefliger, P.,Bertollini, R.. Knowns and unknowns on burden of disease due to chemicals: A systematic review. <i>Environmental Health: A Global Access Science Source</i> . 2011. 10 (1) (no pagination):#pages#	One or more exclusion criteria
L1	Giovinazzo, N.,Inkster, J.,Germain, S.,Colin, D.,Seimbille, Y.. Labeling of a cyclic RGD peptide with two 2-[18F] fluoropyridine prosthetic groups for integrin alphavbeta3 PET imaging. <i>Nuklearmedizin</i> . 2014. 53 (2):A124	One or more exclusion criteria
L1	Set, R.,Shastri, J.. Laboratory aspects of clinically significant rapidly growing mycobacteria. <i>Indian Journal of Medical Microbiology</i> . 2011. 29:343-352	One or more exclusion criteria
L1	Takamizawa, T.,Tsujiimoto, A.,Ishii, R.,Ujiie, M.,Kawazu, M.,Hidari, T.,Suzuki, T.,Miyazaki, M.. Laboratory evaluation of dentin tubule occlusion after use of dentifrices containing stannous fluoride. <i>J Oral Sci</i> . 2019. 61:276-283	One or more exclusion criteria
L1	Levy, S.,Warren, J.,Broffitt, B.,Letuchy, E.,Burns, T.,Gilmore, J. E.,Torner, J.,Janz, K.,Phipps, K.. Lack of association of fluoride intake with girls' childhood bone development assessed by dual-energy x-ray absorptiometry (DXA). <i>Journal of Bone and Mineral</i>	One or more exclusion criteria

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L1	Ribeiro, D. A.,Marques, M. E.,Salvadori, D. M.. Lack of effect of prior treatment with fluoride on genotoxicity of two chemical agents in vitro. <i>Caries Res. 2007. 41:239-43</i>	One or more exclusion criteria
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. <i>J Surg Res. 2014. 192:312-6</i>	One or more exclusion criteria
L1	Sarkar, F. H.,Li, Y.,Wang, Z.,Padhye, S.. Lesson learned from nature for the development of novel anti-cancer agents: Implication of isoflavone, curcumin, and their synthetic analogs. <i>Current Pharmaceutical Design. 2010. 16:1801-1812</i>	One or more exclusion criteria
L1	Klotz, A.,Hughes, K.,McCabe, D.,Cole, J.. Let's Iron OutVR What is Toxic in Here. <i>Clinical Toxicology. 2018. 56 (10):1072-1073</i>	One or more exclusion criteria
L1	Ranjan, R.,Swarup, D.,Bhardwaj, B.,Patra, R. C.. Level of certain micro and macro minerals in blood of cattle from fluoride polluted localities of Udaipur, India. <i>Bulletin of Environmental Contamination and Toxicology. 2008. 81:503-507</i>	One or more exclusion criteria
L1	Naik, R. G.,Dodamani, A. S.,Vishwakarma, P.,Jadhav, H. C.,Khairnar, M. R.,Deshmukh, M. A.,Wadgave, U.. Level of fluoride in soil, grain and water in Jalgaon district, Maharashtra, India. <i>Journal of Clinical and Diagnostic Research. 2017. 11:ZC05-ZC07</i>	One or more exclusion criteria
L1	Makris, K. C.,Andra, S. S.. Limited representation of drinking-water contaminants in pregnancy-birth cohorts. <i>Sci</i>	One or more exclusion

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	<i>Total Environ.</i> 2014. 468-469:165-75	criteria
L1	Hutchings, J.,Kendall, C.,Barr, H.,Stone, N.. Linear discriminant analysis of Raman maps for potential automated histopathology of oesophageal precancer. <i>Lasers in Medical Science.</i> 2009. 24 (5):828	One or more exclusion criteria
L1	Sodhi, R. K.,Singh, N.. Liver X receptor agonist T0901317 reduces neuropathological changes and improves memory in mouse models of experimental dementia. <i>Eur J Pharmacol.</i> 2014. 732:50-9	One or more exclusion criteria
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 water and associated health risks in a semiarid region of Northern China. <i>Ecotoxicol Environ Saf.</i> 2019. 171:274-280	One or more exclusion criteria
L1	Nakahara, Y.,Ozaki, K.,Matsuura, T.. Long-term Hyperglycemia Naturally Induces Dental Caries but Not Periodontal Disease in Type 1 and Type 2 Diabetic Rodents. <i>Diabetes.</i> 2017. 66:2868-2874	One or more exclusion criteria
L1	Matsuura, T.,Shako, N.,Ozaki, K.. Long-term hyperglycemia naturally induces dental caries but not periodontal disease in type-2 diabetic db/db mouse. <i>Experimental Animals.</i> 2017. 66 (Supplement 1):S61	One or more exclusion criteria
L1	Hussain, I.,Ahamad, K. U.,Nath, P.. Low-Cost, Robust, and Field Portable Smartphone Platform Photometric Sensor for Fluoride Level Detection in Drinking Water. <i>Anal Chem.</i> 2017. 89:767-775	One or more exclusion criteria
L1	Huang, Y.,Wang, J.,Tan, Y.,Wang, L.,Lin, H.,Lan, L.,Xiong, Y.,Huang, W.,Shu, W.. Low-mineral direct drinking water in	One or more exclusion criteria

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L1	Zhou, R.,Li, M.,Wang, S.,Wu, P.,Wu, L.,Hou, X.. Low-toxic Mn-doped ZnSe@ZnS quantum dots conjugated with nano-hydroxyapatite for cell imaging. <i>Nanoscale</i> . 2014. 6:14319-25	One or more exclusion criteria
L1	Spillmann, F.,Van Linthout, S.,Miteva, K.,Lorenz, M.,Stangl, V.,Schultheiss, H. P.,Tschöpe, C.. LXR agonism improves TNF- α -induced endothelial dysfunction in the absence of its cholesterol-modulating effects. <i>Atherosclerosis</i> . 2014. 232:1-9	One or more exclusion criteria
L1	McIntyre, D. J.,Madhu, B.,Lee, S. H.,Griffiths, J. R.. Magnetic resonance spectroscopy of cancer metabolism and response to therapy. <i>Radiat Res</i> . 2012. 177:398-435	One or more exclusion criteria
L1	Chandra Shekar, B. R.,Suma, S.,Kumar, S.,Sukhabogi, J. R.,Manjunath, B. C.. Malocclusion status among 15 years old adolescents in relation to fluoride concentration and area of residence. <i>Indian Journal of Dental Research</i> . 2013. 24:1-7	One or more exclusion criteria
L1	Babaei Zarch, A.,Fallah Huseini, H.,Kianbakht, S.,Changaei, P.,Mirjalili, A.,Salehi, J.. Malva sylvestris L. Protects from Fluoride Nephrotoxicity in Rat. <i>Journal of Medicinal Plants</i> . 2017. 16:21-32	One or more exclusion criteria
L1	Kopycka-Kedzierawski, D. T.,Meyerowitz, C.,Litaker, M. S.,Chonowski, S.,Heft, M. W.,Gordan, V. V.,Yardic, R. L.,Madden, T. E.,Reyes, S. C.,Gilbert, G. H.,National Dental, Pbrn Collaborative Group. Management of Dentin	One or more exclusion criteria

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L1	Wu, A. J.. Management of Salivary Hypofunction in Sjogren's Syndrome. <i>Current Treatment Options in Rheumatology</i> . 2015. 1:255-268	One or more exclusion criteria
L1	Samuel, A. R.,Thomas, T.. Management of sensitivity after dental bleaching - A review. <i>International Journal of Pharmacy and Technology</i> . 2016. 8:4857-4864	One or more exclusion criteria
L1	Rischmueller, M.. Management of Sjogren's syndrome. <i>International Journal of Rheumatic Diseases</i> . 2019. 22 (Supplement 3):27-28	One or more exclusion criteria
L1	Fu, H. Z.,Wang, M. H.,Ho, Y. S.. Mapping of drinking water research: A bibliometric analysis of research output during 1992-2011. <i>Science of the Total Environment</i> . 2013. 443:757-765	One or more exclusion criteria
L1	Saini, P.,Khan, S.,Baunthiyal, M.,Sharma, V.. Mapping of fluoride endemic area and assessment of F ⁻¹ accumulation in soil and vegetation. <i>Environmental Monitoring and Assessment</i> . 2013. 185:2001-2008	One or more exclusion criteria
L1	Viswanathan, G.,Jaswanth, A.,Gopalakrishnan, S.,Siva ilango, S.. Mapping of fluoride endemic areas and assessment of fluoride exposure. <i>Sci Total Environ</i> . 2009. 407:1579-87	One or more exclusion criteria
L1	Thakur, N.,Kumar, S. A.,Wagh, D. N.,Das, S.,Pandey, A. K.,Kumar, S. D.,Reddy, A. V.. Matrix supported tailored polymer for solid phase extraction of fluoride from variety of	One or more exclusion criteria

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L1	Deng, H., Ikeda, A., Cui, H., Bartlett, J. D., Suzuki, M.. MDM2-Mediated p21 Proteasomal Degradation Promotes Fluoride Toxicity in Ameloblasts. <i>Cells.</i> 2019. 8:#pages#	One or more exclusion criteria
L1	Becam, J., Gaulier, J. M., Baillif-Couniou, V., Sastre, C., Piercecchi, M. D., Leonetti, G., Pelissier-Alicot, A. L.. MDMA-related deaths: About 3 cases. <i>Toxicologie Analytique et Clinique.</i> 2019. 31 (2 Supplement):S38	One or more exclusion criteria
L1	Kumar, S., Singh, R., Venkatesh, A. S., Udayabhanu, G., Sahoo, P. R.. Medical Geological assessment of fluoride contaminated groundwater in parts of Indo-Gangetic Alluvial plains. <i>Sci Rep.</i> 2019. 9:16243	One or more exclusion criteria
L1	Dissanayake, C. B., Chandrajith, R.. Medical geology in tropical countries with special reference to Sri Lanka. <i>Environ Geochem Health.</i> 2007. 29:155-62	One or more exclusion criteria
L1	Khandare, H. W.. Medical geology: An emerging field of interdisciplinary research on geology and human health. <i>International Journal of ChemTech Research.</i> 2012. 4:1792-1796	One or more exclusion criteria
L1	Zhou, L., Zheng, X., Gu, Z., Yin, W., Zhang, X., Ruan, L., Yang, Y., Hu, Z., Zhao, Y.. Mesoporous NaYbF ₄ @NaGdF ₄ core-shell up-conversion nanoparticles for targeted drug delivery and multimodal imaging. <i>Biomaterials.</i> 2014. 35:7666-78	One or more exclusion criteria
L1	Zhao, Y., Liu, K. T., Xue, Q.. Meta analysis on the effects of water defluoridation measures in China. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2007. 26:434-437	One or more exclusion criteria
L1	Bhardwaj, M., Shashi, A.. Meta-analysis of electrolyte	One or more exclusion

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	imbalance in human fluorosis. <i>Biomedicine and Preventive Nutrition</i> . 2012. 2:294-302	criteria
L1	Costa-Vieira, D.,Monteiro, R.,Martins, M. J.. Metabolic syndrome features: Is there a modulation role by mineral water consumption? a review. <i>Nutrients</i> . 2019. 11 (5) (no pagination):#pages#	One or more exclusion criteria
L1	Qiu, Y.,Zhang, C.,Tu, J.,Zhang, D.. Microbubble-induced sonoporation involved in ultrasound-mediated DNA transfection in vitro at low acoustic pressures. <i>J Biomech</i> . 2012. 45:1339-45	One or more exclusion criteria
L1	He, P.,Domarkas, J.,Cawthorne, C.,Archibald, S.. Microfluidic devices for electrode trapping of [¹⁸ F]fluoride from [¹⁸ O]water and continuous flow radiosynthesis of [¹⁸ F]FLT. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI</i> . 2017. 58:#pages#	One or more exclusion criteria
L1	Ismail, R.,Machness, A.,Van Dam, R. M.,Keng, P. Y.. Microfluidic polymer monoliths for [18F]fluoride concentration, activation and solid phase radiofluorination. <i>Molecular Imaging and Biology</i> . 2012. 1):S1259	One or more exclusion criteria
L1	Philippe, C.,Ungersboeck, J.,Nics, L.,Karanikas, G.,Mitterhauser, M.,Wadsak, W.. Microfluidic preparation of [18F]altanserin for clinical trials. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2013. 2):S421-S422	One or more exclusion criteria
L1	Akula, M.,Collier, T.,Kabalka, G.,Wall, J.,Kennel, S.,Stuckey, A.,LeBlanc, A.. Microfluidic synthesis of	One or more exclusion criteria

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L1	<p>Zhao, J.,Zhu, Y. J.,Wu, J.,Chen, F.. Microwave-assisted solvothermal synthesis and upconversion luminescence of CaF₂:Yb³⁺/Er³⁺ nanocrystals. <i>J Colloid Interface Sci.</i> 2015. 440:39-45</p>	One or more exclusion criteria
L1	<p>Zhao, J.,Zhu, Y. J.,Wu, J.,Chen, F.. Microwave-assisted solvothermal synthesis and upconversion luminescence of CaF₂: Yb³⁺/Er³⁺ nanocrystals. <i>Journal of Colloid and Interface Science.</i> 2015. 440:39-45</p>	One or more exclusion criteria
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L1	<p>Fujimoto, K.,Shimizu, H.,Shimahara, M.,Horiuchi, T.,Kono, R.,Mitsui, G.,Usuda, K.,Kono, K.. MID-term overview of Japan international cooperation agency (JICA) fluorosis mitigation project phase 2 (2011) in Southern India 2. the survey and proposal for skeletal fluorosis. <i>Fluoride.</i> 2012. 45 (3 PART 1):164-165</p>	One or more exclusion criteria
L1	<p>Kono, R.,Shimahara, M.,Ueno, T.,Horiuchi, T.,Shimizu, H.,Fujimoto, K.,Usuda, K.,Kono, K.. MID-term overview of Japan international cooperation agency (JICA) fluorosis</p>	One or more exclusion criteria

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L1	Deavenport-Saman, A.,Britt, A.,Smith, K.,Jacobs, R. A.. Milestones and controversies in maternal and child health: examining a brief history of micronutrient fortification in the US. <i>J Perinatol</i> . 2017. 37:1180-1184	One or more exclusion criteria
L1	Xie, Y. L.,Zhang, B.,Jing, L.. MiR-125b blocks Bax/Cytochrome C/Caspase-3 apoptotic signaling pathway in rat models of cerebral ischemia-reperfusion injury by targeting p53. <i>Neurol Res</i> . 2018. 40:828-837	One or more exclusion criteria
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L1	Bonotto, D. M.,Oliveira, A. M. M. A. D.. Mobility indices and doses from ²¹⁰ Po and ²¹⁰ Pb activity concentrations data in Brazilian spas groundwaters. <i>Journal of Environmental Radioactivity</i> . 2017. 172:15-23	One or more exclusion criteria
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L1	Oruc, N.. Occurrence and problems of high fluoride waters in Turkey: an overview. <i>Environ Geochem Health</i> . 2008. 30:315-23	One or more exclusion criteria
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. <i>Critical Reviews in Environmental Science and Technology</i> . 2019. 49:2359-2396	One or more exclusion criteria
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L1	Donaldson, M.,Goodchild, J. H.. Oral health of the methamphetamine abuser. <i>Am J Health Syst Pharm</i> . 2006. 63:2078-82	One or more exclusion criteria
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L1	Gonzalez, S.,Sung, H.,Sepulveda, D.,Gonzalez, M. J.,Molina, C.. Oral manifestations and their treatment in Sjogren's syndrome. <i>Oral Diseases.</i> 2014. 20:153-161	One or more exclusion criteria
L1	Aguilar-Díaz, F. C.,Irigoyen-Camacho, M. E.,Borges-Yáñez, S. A.. Oral-health-related quality of life in schoolchildren in an endemic fluorosis area of Mexico. <i>Qual Life Res.</i> 2011. 20:1699-706	One or more exclusion criteria
L1	Zorc, B.,Pavic, K.. Organofluorine drugs. [Croatian]. <i>Farmaceutski Glasnik.</i> 2018. 74:351-360	One or more exclusion criteria
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L1	Choubisa, S. L.. Osteo-dental fluorosis in domestic animals living in areas with high fluoride in drinking water of Rajasthan, India. <i>Fluoride.</i> 2012. 45 (3 PART 1):158	One or more exclusion criteria
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L1	Tamer, M. N.,Kale Köroğlu, B.,Arslan, C.,Akdoğan, M.,Köroğlu, M.,Cam, H.,Yildiz, M.. Osteosclerosis due to endemic fluorosis. <i>Sci Total Environ</i> . 2007. 373:43-8	One or more exclusion criteria
L1	Uppal, S.,Bajaj, Y.,Coatesworth, A. P.. Otosclerosis 2: The medical management of otosclerosis. <i>International Journal of Clinical Practice</i> . 2010. 64:256-265	One or more exclusion criteria
L1	Babcock, T. A.,Liu, X. Z.. Otosclerosis: From Genetics to Molecular Biology. <i>Otolaryngologic Clinics of North America</i> . 2018. 51:305-318	One or more exclusion criteria
L1	Liao, M.,Liu, J.,Tang, Z. Z.,Huang, L. R.,Ning, R. J.,Zeng, X. P.. Outcome analysis of endemic fluorosis control in Guangxi in 2006. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2008. 27:300-302	One or more exclusion criteria
L1	Huang, C. Q.,Wang, C. H.,Zhang, X. D.,Xu, H. W.,Tang, H. Y.,Lu, Z. M.,Zhang, A. J.,Zhang, Y. L.. Outcome analysis of surveillance on endemic fluorosis during thr period of 1991 to 2006 in Jilin Province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2009. 28:424-428	One or more exclusion criteria
L1	Yu, S. Q.,Liao, Y. J.,Sha, J. Y.. Outcome analysis on endemic flourosis control in Gansu province in 2006. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2009. 28:187-190	One or more exclusion criteria

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L1	Wu, Z. M., Li, J., Wang, Z. H., Zhang, X. D., Han, L. L., Qiao, X. Y., Li, P. F., Jing, Y. L.. Outcome analysis on screening of drinking water source with high fluoride and the condition of the water-improving projects in Shanxi province in 2007. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:316-318	One or more exclusion criteria
L1	Liu, Y., Li, X. F., Yue, Y. T., Zheng, H. M., Yu, B., Yu, H. Y., Hao, Z. Y.. Outcome assessment of health education on endemic diseases in Henan province in 2010. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2013. 32:104-108	One or more exclusion criteria
L1	Niu, Q.. Overview of the Relationship Between Aluminum Exposure and Health of Human Being. <i>Adv Exp Med Biol</i> . 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. <i>Cancer Medicine</i> . 2018. 7 (Supplement 1):33	One or more exclusion criteria
L1	Jeppesen, T. E., Kristensen, L. K., Nielsen, C. H., Petersen, L. C., Kristensen, J. B., Behrens, C., Madsen, J., Kjaer, A.. Oxime Coupling of Active Site Inhibited Factor Seven with a Nonvolatile, Water-Soluble Fluorine-18 Labeled Aldehyde. <i>Bioconjug Chem</i> . 2019. 30:775-784	One or more exclusion criteria
L1	Foulkes, R. G.. Paradigms and public health policy versus	One or more exclusion

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L1	Shashi, A.,Singla, S.. Parathyroid function in osteofluorosis. <i>World Journal of Medical Sciences</i> . 2013. 8:67-73	One or more exclusion criteria
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. <i>Swed Dent J</i> . 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. <i>Rev Environ Contam Toxicol</i> . 2008. 192:29-66	One or more exclusion criteria
L1	Khan, M. S.,Naz, F.,Javid, R.,Mosby, T. T.,Assaf, N.. Pattern of nutritional deficiencies in childhood cancer patients-experience from a large cancer hospital in Pakistan. <i>Pediatric Blood and Cancer</i> . 2016. 63 (Supplement 3):S282	One or more exclusion criteria
L1	Stepanova, N. V.,Valeeva, E. R.,Ziyatdinova, A. I.,Fomina, S. F.. Peculiarities of children's risk assessment on ingestion of chemicals with drinking water. <i>Research Journal of Pharmaceutical, Biological and Chemical Sciences</i> . 2016. 7:1677-1681	One or more exclusion criteria
L1	Zhu, Z.,Wang, T.,Meng, J.,Wang, P.,Li, Q.,Lu, Y.. Perfluoroalkyl substances in the Daling River with concentrated fluorine industries in China: seasonal	One or more exclusion criteria

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L1	Badi, M. Y.,Azari, A.,Esrafil, A.,Ahmadi, E.,Gholami, M.. Performance evaluation of magnetized multiwall carbon nanotubes by iron oxide nanoparticles in removing fluoride from aqueous solution. [Persian]. <i>Journal of Mazandaran University of Medical Sciences.</i> 2015. 25:128-142	One or more exclusion criteria
L1	Vandana, K. L.,George, P.,Cobb, C. M.. Periodontal changes in fluorosed and nonfluorosed teeth by scanning electron microscopy. <i>Fluoride.</i> 2007. 40:128-133	One or more exclusion criteria
L1	Pan, D.,Yan, Y.,Yang, R.,Xu, Y. P.,Chen, F.,Wang, L.,Luo, S.,Yang, M.. PET imaging of prostate tumors with 18F-Al-NOTA-MATBBN. <i>Contrast Media Mol Imaging.</i> 2014. 9:342-8	One or more exclusion criteria
L1	Morana, G.,Piccardo, A.,Luisa Garre, M.,Rossi, A.. PET/MR of paediatric brain tumours. <i>Cancer Imaging. Conference: 16th Annual Teaching Course of the International Cancer Imaging Society, ICIS.</i> 2016. 16:#pages#	One or more exclusion criteria
L1	Wallat, J. D.,Harrison, J. K.,Pokorski, J. K.. pH Responsive Doxorubicin Delivery by Fluorous Polymers for Cancer Treatment. <i>Mol Pharm.</i> 2018. 15:2954-2962	One or more exclusion criteria
L1	Chander, V.,Sharma, B.,Negi, V.,Aswal, R. S.,Singh, P.,Singh, R.,Dobhal, R.. Pharmaceutical compounds in drinking water. <i>Journal of Xenobiotics.</i> 2016. 6 (1) (no pagination):#pages#	One or more exclusion criteria
L1	Lin, H. H.,Lin, A. Y.. Photocatalytic oxidation of 5-fluorouracil and cyclophosphamide via UV/TiO ₂ in an	One or more exclusion

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	aqueous environment. <i>Water Res.</i> 2014. 48:559-68	criteria
L1	Wang, H. X.,Zhu, L. N.,Guo, F. Q.. Photoelectrocatalytic degradation of atrazine by boron-fluorine co-doped TiO(2) nanotube arrays. <i>Environ Sci Pollut Res Int.</i> 2019. 26:33847-33855	One or more exclusion criteria
L1	Macpherson, L. M. D.,Conway, D. I.,Gilmour, W. H.,Petersson, L. G.,Stephen, K. W.. Photographic assessment of fluorosis in children from naturally fluoridated Kungsbacka and non-fluoridated Halmstad, Sweden. <i>Acta Odontologica Scandinavica.</i> 2007. 65:149-155	One or more exclusion criteria
L1	Sirtori, C.,Zapata, A.,Gernjak, W.,Malato, S.,Aguera, A.. Photolysis of flumequine: Identification of the major phototransformation products and toxicity measures. <i>Chemosphere.</i> 2012. 88:627-634	One or more exclusion criteria
L1	Nirmala, B.,Suchetan, P. A.,Darshan, D.,Sudha, A. G.,Lohith, T. N.,Suresh, E.,Mamtha,. Physico-chemical analysis of selected groundwater samples of Tumkur district, Karnataka. <i>International Journal of ChemTech Research.</i> 2013. 5:288-292	One or more exclusion criteria
L1	Farronato, M.,Cossellu, G.,Farronato, G.,Inchingolo, F.,Blasi, S.,Angiero, F.. Physico-chemical characterization of a smart thermo-responsive fluoride-releasing poloxamer-based gel. <i>Journal of Biological Regulators and Homeostatic Agents.</i> 2019. 33:1309-1314	One or more exclusion criteria
L1	Foka, F. E. T.,Yah, C. S.,Bissong, M. E. A.. Physico-chemical properties and microbiological quality of borehole water in four crowded areas of benin city, nigeria, during	One or more exclusion criteria

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L1	Singh, A. K.,Das, S.,Singh, S.,Pradhan, N.,Gajamer, V. R.,Kumar, S.,Lepcha, Y. D.,Tiwari, H. K.. Physicochemical parameters and alarming coliform count of the potable water of Eastern Himalayan state Sikkim: An indication of severe fecal contamination and immediate health risk. <i>Frontiers in Cell and Developmental Biology</i> . 2019. 7 (AUG) (no pagination):#pages#	One or more exclusion criteria
L1	Iagaru, A.,Young, P.,Mittra, E.,Dick, D. W.,Herfkens, R.,Gambhir, S. S.. Pilot prospective evaluation of 99mTc-MDP scintigraphy, 18F NaF PET/CT, 18F FDG PET/CT and whole-body MRI for detection of skeletal metastases. <i>Clin Nucl Med</i> . 2013. 38:e290-6	One or more exclusion criteria
L1	Zhong, B.,Wang, L.,Liang, T.,Xing, B.. Pollution level and inhalation exposure of ambient aerosol fluoride as affected by polymetallic rare earth mining and smelting in Baotou, north China. <i>Atmospheric Environment</i> . 2017. 167:40-48	One or more exclusion criteria
L1	He, X.,Li, P.,Wu, J.,Wei, M.,Ren, X.,Wang, D.. Poor	One or more exclusion

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L1	Lahna, D.,Woltjer, R.,Grinstead, J.,Boespflug, E. L.,Schwartz, D.,Kaye, J. A.,Rooney, W. D.,Silbert, L. C.. Postmortem 7t Mri for Guided Histology and Tissue Segmentation. <i>Alzheimer's and Dementia</i> . 2018. 14 (7 Supplement):P53	One or more exclusion criteria
L1	Burnett, G. R.,Gallob, J. T.,Milleman, K. R.,Mason, S.,Patil, A.,Budhawant, C.,Milleman, J. L.. Potassium oxalate oral rinses for long-term relief from dentinal hypersensitivity: Three randomised controlled studies. <i>J Dent</i> . 2018. 70:23-30	One or more exclusion criteria
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L1	Lung, S. C.,Cheng, H. W.,Fu, C. B.. Potential exposure and risk of fluoride intakes from tea drinks produced in Taiwan. <i>Journal of Exposure Science & Environmental Epidemiology</i> . 2008. 18:158-66	One or more exclusion criteria
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. <i>Environmental</i>	One or more exclusion criteria

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L1	Gai, Y., Altine, B., Han, N., Lan, X.. Preclinical evaluation of a ¹⁸ F-labeled phosphatidylinositol 3-kinase inhibitor for breast cancer imaging. <i>Journal of Nuclear Medicine. Conference</i> . 2019. 60:#pages#	One or more exclusion criteria
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.. Preclinical Evaluation of a Fluorine-18 ((¹⁸ F)-Labeled Phosphatidylinositol 3-Kinase Inhibitor for Breast Cancer Imaging. <i>Mol Pharm</i> . 2019. 16:4563-4571	One or more exclusion criteria
L1	Podgorski, J. E., Labhasetwar, P., Saha, D., Berg, M.. Prediction Modeling and Mapping of Groundwater Fluoride Contamination throughout India. <i>Environmental Science & Technology</i> . 2018. 52:9889-9898	One or more exclusion criteria
L1	Han, I. H.. Pregnancy and spinal problems. <i>Current Opinion in Obstetrics and Gynecology</i> . 2010. 22:477-481	One or more exclusion criteria
L1	Datta, A. S., Singh, R., Basu, D., Lahiri, S. C.. Preliminary clinical investigation on fluoride contamination in Nalhati subdivision (West Bengal); possible structural changes of water due to fluoride ion and related clinical aspects. <i>Journal of the Indian Chemical Society</i> . 2016. 93:1383-1388	One or more exclusion criteria
L1	Martínez-Acuña, M. I., Mercado-Reyes, M., Alegría-Torres, J. A., Mejía-Saavedra, J. J.. Preliminary human health risk assessment of arsenic and fluoride in tap water from Zacatecas, México. <i>Environ Monit Assess</i> . 2016. 188:476	One or more exclusion criteria

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L1	Dam, J.,Langkjaer, N.,Baun, C.,Olsen, B.. Preparation and evaluation of (18)F AIF-NOTA-NOC for PET imaging of neuroendocrine tumors. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 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. <i>J Radioanal Nucl Chem</i> . 2011. 287:93-101	One or more exclusion criteria
L1	Lakshminarayanan, N.,Arjun, G.,Rajan, M. G. R.. Preparation of 18F-Fluoroethyltyrosine: Preliminary studies. <i>Indian Journal of Nuclear Medicine</i> . 2011. 1):S43	One or more exclusion criteria
L1	Li, M. H.,Chu, H. H.,Chang, H. C.,Feng, C. F.. Preparing of [¹⁸ F]INER-1577 as histone deacetylase (HDAC2) imaging agent for AD. <i>Molecular Imaging and Biology</i> . 2016. 18 (2 Supplement):S592-S593	One or more exclusion criteria
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. <i>Trop Med Int Health</i> . 2013. 18:222-9	One or more exclusion criteria
L1	Isaac, A.,Silvia, W. D. C. R.,Somanna, S. N.,Mysorekar, V.,Narayana, K.,Srikantiah, P.. Prevalence and manifestations of water-born fluorosis among schoolchildren in Kaiwara village of India: A preliminary study. <i>Asian Biomedicine</i> . 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	One or more exclusion criteria

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L1	Pretty, I. A.,Boothman, N.,Morris, J.,MacKay, L.,Liu, Z.,McGrady, M.,Goodwin, M.. Prevalence and severity of dental fluorosis in four English cities. <i>Community Dent Health.</i> 2016. 33:292-296	One or more exclusion criteria
L1	Beltrán-Aguilar, E. D.,Barker, L.,Dye, B. A.. Prevalence and severity of dental fluorosis in the United States, 1999-2004. <i>NCHS Data Brief.</i> 2010. #volume#:1-8	One or more exclusion criteria
L1	Fan, Z.,Gao, Y.,Wang, W.,Gong, H.,Guo, M.,Zhao, S.,Liu, X.,Yu, B.,Sun, D.. Prevalence of Brick Tea-Type Fluorosis in the Tibet Autonomous Region. <i>J Epidemiol.</i> 2016. 26:57-63	One or more exclusion criteria
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. <i>Environmental Monitoring and Assessment.</i> 2010. 160:141-155	One or more exclusion criteria
L1	Shekar, C.,Cheluvaiah, M. B.,Namile, D.. Prevalence of dental caries and dental fluorosis among 12 and 15 years old school children in relation to fluoride concentration in drinking water in an endemic fluoride belt of Andhra Pradesh. <i>Indian J Public Health.</i> 2012. 56:122-8	One or more exclusion criteria
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. <i>European Journal of</i>	One or more exclusion criteria

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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]. <i>Chinese Journal of Endemiology</i> . 2013. 32:309-311	One or more exclusion criteria
L1	Kotecha, P. V.,Patel, S. V.,Bhalani, K. D.,Shah, D.,Shah, V. S.,Mehta, K. G.. Prevalence of dental fluorosis & dental caries in association with high levels of drinking water fluoride content in a district of Gujarat, India. <i>Indian Journal of Medical Research</i> . 2012. 135:873-877	One or more exclusion criteria
L1	Sebastian, S. T.,Soman, R. R.,Sunitha, S.. Prevalence of dental fluorosis among primary school children in association with different water fluoride levels in Mysore district, Karnataka. <i>Indian Journal of Dental Research</i> . 2016. 27:151-4	One or more exclusion criteria
L1	Khatib, N.,Meghe, A. D.. Prevalence of dental fluorosis among primary school children in rural areas of INDIA. <i>Fluoride</i> . 2012. 45 (3 PART 1):185	One or more exclusion criteria
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. <i>Biosciences Biotechnology Research Asia</i> . 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	One or more exclusion criteria

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L1	Pandey, A.. Prevalence of fluorosis in an endemic village in central India. <i>Trop Doct</i> . 2010. 40:217-9	One or more exclusion criteria
L1	Jaganmohan, P.,Narayana Rao, S. V. L.,Sambasiva Rao, K. R. S.. Prevalence of high fluoride concentration in drinking water in Nellore District, A.p., India: A biochemical study to develop the relation to renal failures. <i>World Journal of Medical Sciences</i> . 2010. 5:45-48	One or more exclusion criteria
L1	Sharma, J. D.,Sohu, D.,Jain, P.. Prevalence of neurological manifestations in a human population exposed to fluoride in drinking water. <i>Fluoride</i> . 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. <i>Rocz Panstw Zakl Hig</i> . 2015. 66:379-82	One or more exclusion criteria
L1	Syme, S. L.. Preventing disease and promoting health: The need for some new thinking. <i>Sozial- und Praventivmedizin</i> . 2006. 51:247-248	One or more exclusion criteria
L1	Susheela, A. K.,Toteja, G. S.. Prevention & control of fluorosis & linked disorders: Developments in the 21 st Century - Reaching out to patients in the community & hospital settings for recovery. <i>Indian Journal</i>	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. <i>Lasers in Medical Science</i> . 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. <i>Caries research</i> . 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. <i>Environmental Pollution</i> . 2017. 222:118-125	One or more exclusion criteria
L1	Zhang, L. E.,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. <i>Environ Pollut</i> . 2017. 222:118-125	One or more exclusion criteria
L1	Soderquist, C. Z.,McNamara, B. K.,Fisher, D. R.. Production of high-purity radium-223 from legacy actinium-beryllium neutron sources. <i>Curr Radiopharm</i> . 2012. 5:244-52	One or more exclusion criteria

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L1	Holmquist, H.,Schellenberger, S.,van der Veen, I.,Peters, G. M.,Leonards, P. E. G.,Cousins, I. T.. Properties, performance and associated hazards of state-of-the-art durable water repellent (DWR) chemistry for textile finishing. <i>Environment International</i> . 2016. 91:251-264	One or more exclusion criteria
L1	Awad, A.,Cipriani, A.. Prophylactic mood stabilization: What is the evidence for lithium exposure in drinking water?. <i>Bipolar Disorders</i> . 2017. 19:601-602	One or more exclusion criteria
L1	Bruton, T. A.,Blum, A.. Proposal for coordinated health research in PFAS-contaminated communities in the United States. <i>Environmental Health: A Global Access Science Source</i> . 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, F.,Simon, B.,Schild, H. H.. Protective effect on tissue using dental waterjet and dexpanthenol rinsing solution during radiotherapy in head and neck tumor patients. <i>Strahlentherapie und Onkologie</i> . 2016. 192 (1 Supplement 1):66	One or more exclusion criteria
L1	Rameshrad, M.,Razavi, B. M.,Hosseinzadeh, H.. Protective effects of green tea and its main constituents against	One or more exclusion criteria

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L1	Das, N.,Das, A.,Sarma, K. P.,Kumar, M.. Provenance, prevalence and health perspective of co-occurrences of arsenic, fluoride and uranium in the aquifers of the Brahmaputra River floodplain. <i>Chemosphere</i> . 2018. 194:755-772	One or more exclusion criteria
L1	Qu, W.,Zheng, W.,Spencer, P.,Zheng, J.,Yang, L.,Han, F.,Yan, L.,Ma, W.,Zhou, Y.,Zheng, Y.,Wang, Y.. Public health concerns arising from interventions designed to circumvent polluted surface drinking water in Shenqiu County, Henan, China. <i>The Lancet</i> . 2017. 390 (SPEC.ISS 1):87	One or more exclusion criteria
L1	Berry, C.. Public health impact of food: Quantity, quality, supplements and appetites. <i>Toxicology Letters</i> . 2013. 1):S2	One or more exclusion criteria
L1	Schwenzer, N. F.,Schraml, C.,Muller, M.,Brendle, C.,Sauter, A.,Spengler, W.,Pfannenbergl, A. C.,Claussen, C. D.,Schmidt, H.. Pulmonary lesion assessment: Comparison of whole-body hybrid MR/PET and PET/CT imaging - Pilot study. <i>Radiology</i> . 2012. 264:551-558	One or more exclusion criteria
L1	Deepa, P.,Arun, R. N.. Quality assessment of drinking water in different localities of Manjeri. <i>International Journal of Pharmaceutical Sciences Review and Research</i> . 2013.	One or more exclusion criteria

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L1	de Carvalho, A. M.,Duarte, M. C.,Ponezi, A. N.. Quality assessment of sulfurous thermal waters in the city of Pocos de caldas, Minas gerais, Brazil. <i>Environmental Monitoring & Assessment.</i> 2015. 187:563	One or more exclusion criteria
L1	Thitame, S. N.,Somasundaram, K. V.. Quality of drinking water and associated health risks in rural Ahmednagar, Maharashtra, India. <i>Journal of Chemical and Pharmaceutical Research.</i> 2015. 7:660-663	One or more exclusion criteria
L1	Hayat, E.,Baba, A.. Quality of groundwater resources in Afghanistan. <i>Environmental Monitoring and Assessment.</i> 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. <i>Mol Imaging Biol.</i> 2012. 14:348-54	One or more exclusion criteria
L1	Tomlinson, R.,Silva, M. J.,Shoghi, K. I.. Quantification of skeletal blood flow and fluoride metabolism in rodents. <i>Molecular Imaging and Biology.</i> 2010. 2):S1412	One or more exclusion criteria
L1	Klomp, D.,van Laarhoven, H.,Scheenen, T.,Kamm, Y.,Heerschap, A.. Quantitative ¹⁹ F MR spectroscopy at 3 T to detect heterogeneous capecitabine metabolism in human liver. <i>NMR in Biomedicine.</i> 2007. 20:485-92	One or more exclusion criteria
L1	Fernández Mdel, M.,Wille, S. M.,Kummer, N.,Di Fazio, V.,Ruyssinckx, E.,Samyn, N.. Quantitative analysis of 26 opioids, cocaine, and their metabolites in human blood by ultra performance liquid chromatography-tandem mass	One or more exclusion criteria

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L1	Jiang, F.,Lei, P.,Chen, Y.,Zuu, X.,Lao, P.,Pan, X.. Quantitative computed tomography measurement skeletal fluorosis rabbits bone density and the correlation with bone injury. [Chinese]. <i>Chinese Journal of Endemiology.</i> 2017. 36:414-417	One or more exclusion criteria
L1	Maggitti, A. L.,Blum, L.,McMullin, M.. Quantitative testing for polychlorinated biphenyls (PCBs) in human serum utilizing gas chromatography tandem mass spectrometry (GC-MS/MS). <i>Clinical Chemistry.</i> 2016. 62 (10 Supplement 1):S112	One or more exclusion criteria
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. M.,Womack, D. S.,Wickremasinghe, R.. 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. <i>Environ Monit Assess.</i> 2016. 188:548	One or more exclusion criteria
L1	Taddei, C.,Pike, V.. Radiofluorination of a COX-1 specific ligand based on two nucleophilic addition strategies. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2019. 62 (Supplement 1):S115-S116	One or more exclusion criteria
L1	Lee, S. H.,Park, J. K.,Lee, S. Y.,Lee, J.,Ido, T.. Radiolabeling of SUV size liposome with hexadecyl-4- ¹⁸ F]fluorobenzoate (¹⁸ F] HFB)	One or more exclusion criteria

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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 [¹¹ C]NS8880 and its evaluation in the rat. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 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. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2019. 62 (Supplement 1):S577	One or more exclusion criteria
L1	Olberg, D.,Arukwe, J.,Solbakken, M.,Cuthbertson, A.,Qu, H.,Kristian, A.,Hjelstuen, O.. Radiosynthesis and biodistribution of cyclic RGD peptides conjugated with a novel [¹⁸ F] fluorinated N-methylaminooxy containing prosthetic group. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2009. 1):S32	One or more exclusion criteria
L1	Graf, K.,Hellman, M.,Kavathas, S.,Dewey, S.,Schiffer, W.,Subramaniam, G.,Chaly, T.. Radiosynthesis and in vivo evaluation of [¹⁸ F]C8-ceramide analogues as potential tumor imaging agents. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 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,	One or more exclusion criteria

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L1	Brooks, A. F.,Rodnick, M. E.,Fawaz, M. V.,Desmond, T. J.,Scott, P. J. H.. Radiosynthesis of [¹⁸ F]gem-difluoroalkenes and [¹⁸ F]CF ₃ Groups- Preparation of [¹⁸ F]ansoprazole and related analogs for PET imaging of tau neurofibrillary tangles. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2013. 1):S29	One or more exclusion criteria
L1	Malik, N.,Zlatopolskiy, B.,Voelter, W.,Solbach, C.,Machulla, H. J.,Reske, S. N.. Radiosynthesis of a new PSMA targeting ligand (¹⁸ F]FPy-DUPA-Pep). <i>NuklearMedizin.</i> 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 [¹⁸ F]PSS232 with protic solvent additives. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2017. 60 (Supplement 1):S289	One or more exclusion criteria
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L1	Villeneuve, P. J.,Morrison, H. I.,Lane, R.. Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. <i>Health Phys</i> . 2007. 92:157-69	One or more exclusion criteria
L1	Old, O. J.,Isabelle, M.,Lloyd, G.,Kendall, C.,Barr, H.,Stone, N.. Raman mapping for pathology classification: The need for speed. <i>Gut</i> . 2015. 1):A485-A486	One or more exclusion criteria
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L1	Valdora, F., Houssami, N., Rossi, F., Calabrese, M., Tagliafico, A. S.. Rapid review: radiomics and breast cancer. <i>Breast Cancer Res Treat</i> . 2018. 169:217-229	One or more exclusion criteria
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). <i>EJNMMI Radiopharm Chem</i> . 2019. 5:1	One or more exclusion criteria
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L1	Tripathi, M., Gupta, R., Sharma, U. D.. Recovery of adverse effects induced by fluoride after ascorbic acid treatment in <i>Channa punctatus</i> (bloch). <i>Journal of Ecophysiology and Occupational Health</i> . 2008. 8:147-152	One or more exclusion criteria

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L1	Ishibashi, K.,Kawasaki, K.,Ishiwata, K.,Ishii, K.. Reduced uptake of 18F-FDG and 15O-H2O in Alzheimer's disease-related regions after glucose loading. <i>J Cereb Blood Flow Metab</i> . 2015. 35:1380-5	One or more exclusion criteria
L1	Indermitte, E.,Saava, A.,Karro, E.. Reducing exposure to high fluoride drinking water in Estonia-a countrywide study. <i>International Journal of Environmental Research & Public Health [Electronic Resource]</i> . 2014. 11:3132-42	One or more exclusion criteria
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L1	Manne, M.,Validandi, V.,Khandare, A. L.. Reduction of fluoride toxicity by tamarind components: An in silico study. <i>Fluoride</i> . 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. <i>Toxicology Letters</i> . 2009. 1):S236	One or more exclusion criteria
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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. <i>Journal of Nanjing Medical University</i> . 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. <i>Contrast Media and Molecular Imaging</i> . 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. <i>Progress in Orthodontics</i> . 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. <i>Chemosphere</i> . 2014. 117:679-691	One or more exclusion criteria
L1	Jha, A. K.,Mishra, B.. Removal of fluoride by bentonite minerals of Rajmahal Hills. <i>Journal of the Indian Chemical Society</i> . 2012. 89:519-521	One or more exclusion criteria
L1	Solangi, I. B.,Memon, S.,Bhanger, M. I.. Removal of	One or more exclusion

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L1	Akafu, T.,Chimdi, A.,Gomoro, K.. Removal of Fluoride from Drinking Water by Sorption Using Diatomite Modified with Aluminum Hydroxide. <i>J Anal Methods Chem</i> . 2019. 2019:4831926	One or more exclusion criteria
L1	Ganvir, V.,Das, K.. Removal of fluoride from drinking water using aluminum hydroxide coated rice husk ash. <i>Journal of Hazardous Materials</i> . 2011. 185:1287-94	One or more exclusion criteria
L1	Ramaiah, K. P.,Satyasri, D.,Sridhar, S.,Krishnaiah, A.. Removal of hazardous chlorinated VOCs from aqueous solutions using novel ZSM-5 loaded PDMS/PVDF composite membrane consisting of three hydrophobic layers. <i>J Hazard Mater</i> . 2013. 261:362-71	One or more exclusion criteria
L1	Tran, H. N.,Nguyen, H. C.,Woo, S. H.,Nguyen, T. V.,Vigneswaran, S.,Hosseini-Bandegharaei, A.,Rinklebe, J.,Kumar Sarmah, A.,Ivanets, A.,Dotto, G. L.,Bui, T. T.,Juang, R. S.,Chao, H. P.. Removal of various contaminants from water by renewable lignocellulose-derived biosorbents: a comprehensive and critical review. <i>Critical Reviews in Environmental Science and Technology</i> . 2019. 49:2155-2219	One or more exclusion criteria
L1	Sen, S. K.,Rattan, R.,Meenakshi, V.,Sripradha,,Kumar, A.,Nanda, N.. Renal stones analysis: Our experience at Pondicherry institute of medical sciences. <i>Biomedicine (India)</i> . 2009. 29:284-285	One or more exclusion criteria
L1	Rocha, M. J. A.,Tazinafo, L. F.,Basso, P. J.,Silva, M. F.. Replacing laboratory animals by alternative material for	One or more exclusion criteria

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L1	Whelan, E. M.. Reply. <i>MedGenMed Medscape General Medicine</i> . 2008. 10 (4) (no pagination):#pages#	One or more exclusion criteria
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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]. <i>Chinese Journal of Endemiology</i> . 2008. 27:671-672	One or more exclusion criteria
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L1	Ema, M.,Naya, M.,Yoshida, K.,Nagaosa, R.. Reproductive and developmental toxicity of degradation products of refrigerants in experimental animals. <i>Reprod Toxicol</i> . 2010. 29:1-9	One or more exclusion criteria
L1	Hong, F.,Cao, Y.,Yang, D.,Wang, H.. Research on the effects of fluoride on child intellectual development under different environmental conditions. <i>Fluoride</i> . 2008. 41:156-160	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. <i>Br J Radiol</i> . 2018. 91:20170640	One or more exclusion criteria
L1	Farooqi, A.,Zafar, M. I.. Response to "Co-occurrence of arsenic and fluoride in the groundwater of Punjab, Pakistan: source discrimination and health risk assessment" by Rasool et al. 2015. <i>Environ Sci Pollut Res Int</i> . 2016. 23:13578-80	One or more exclusion criteria
L1	Gartenschläger, M.,Schreckenberger, M.,Buchholz, H. G.,Reiner, I.,Beutel, M. E.,Adler, J.,Michal, M.,Jing, C.,Cui, J.,Huang, Y.,Li, A.. Resting Brain Activity Related to Fabrication, characterization, and application of a composite adsorbent for simultaneous removal of arsenic and fluoride. <i>Mindfulness (N Y)</i> . 2017. 8:1009-1017 Dispositional Mindfulness: a PET Study	One or more exclusion criteria
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L1	Zhang, H. M.,Luo, Z. W.,Nie, J.,Wen, T. A.,Ping, B.. Retrospective analysis of prevention of fluorosis of coal-burning type in Longli County, Guizhou. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:713-715	One or more exclusion criteria

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L1	Gebrewold, M. A.. Review article: Neurological complications of endemic skeletal fluorosis in Ethiopia. <i>European Journal of Neurology.</i> 2012. 19 (SUPPL.1):801	One or more exclusion criteria
L1	Mohapatra, M.,Anand, S.,Mishra, B. K.,Giles, D. E.,Singh, P.. Review of fluoride removal from drinking water. <i>Journal of Environmental Management.</i> 2009. 91:67-77	One or more exclusion criteria
L1	Carton, R. J.. Review of the 2006 United States National Research Council report: Fluoride in drinking water. <i>Fluoride.</i> 2006. 39:163-172	One or more exclusion criteria
L1	Satur, J. G.,Gussy, M. G.,Morgan, M. V.,Calache, H.,Wright, C.. Review of the evidence for oral health promotion effectiveness. <i>Health Education Journal.</i> 2010. 69:257-266	One or more exclusion criteria
L1	Jarquín-Yanez, L.,Mejía-Saavedra, J.,Molina-Frechero, N.,Pozos-Guillen, A.,Alvarez, G.. Risk assessment by exposure to fluorine through water consumption, by determining susceptibility biomarkers and effect in child population of San Luis Potosí. <i>Toxicology Letters.</i> 2016. 259 (Supplement 1):S123-S124	One or more exclusion criteria
L1	Guissouma, W.,Hakami, O.,Al-Rajab, A. J.,Tarhouni, J.. Risk assessment of fluoride exposure in drinking water of Tunisia. <i>Chemosphere.</i> 2017. 177:102-108	One or more exclusion criteria
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L1	Arulazhagan, P.,Vasudevan, N.. Role of a moderately halophilic bacterial consortium in the biodegradation of polyaromatic hydrocarbons. <i>Mar Pollut Bull</i> . 2009. 58:256-62	One or more exclusion criteria
L1	Liu, Q. B.,Liu, X. B.,Wang, S. J.,Liu, X. H.,Yu, B.,Jiang, Z. L.,Wang, Z. J.,Zhou, M. R.,Zhang, X. K.,Tian, S. C.. Role of brick tea with low-fluoride level in prevention of tea type fluorosis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:156-158	One or more exclusion criteria
L1	Daiwile, A. P.,Tarale, P.,Sivanesan, S.,Naoghare, P. K.,Bafana, A.,Parmar, D.,Kannan, K.. Role of fluoride induced epigenetic alterations in the development of skeletal fluorosis. <i>Ecotoxicol Environ Saf</i> . 2019. 169:410-417	One or more exclusion criteria
L1	Chen, Y.,Li, H.,Li, M.,Niu, S.,Wang, J.,Shao, H.,Li, T.,Wang, H.. Salvia miltiorrhiza polysaccharide activates T Lymphocytes of cancer patients through activation of TLRs mediated -MAPK and -NF-κB signaling pathways. <i>J Ethnopharmacol</i> . 2017. 200:165-173	One or more exclusion criteria
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	fluorosis in Hunyuan county of Shanxi province: An analysis of monitoring results. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:309-311	criteria
L1	Khandare, H. W.. Scenario of nitrate contamination in groundwater: Its causes and prevention. <i>International Journal of ChemTech Research</i> . 2013. 5:1921-1926	One or more exclusion criteria
L1	Allukian, M.,Carter-Pokras, O. D.,Gooch, B. F.,Horowitz, A. M.,Iida, H.,Jacob, M.,Kleinman, D. V.,Kumar, J.,Maas, W. R.,Pollick, H.,Rozier, R. G.. Science, Politics, and Communication: The Case of Community Water Fluoridation in the US. <i>Annals of Epidemiology</i> . 2018. 28:401-410	One or more exclusion criteria
L1	Kudinov, K. A.,Cooper, D. R.,Ha, J. K.,Hill, C. K.,Nadeau, J. L.,Seuntjens, J. P.,Bradforth, S. E.. Scintillation Yield Estimates of Colloidal Cerium-Doped LaF(3) Nanoparticles and Potential for "Deep PDT". <i>Radiat Res</i> . 2018. 190:28-36	One or more exclusion criteria
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L1	Zhu, C.,Bai, G.,Liu, X.,Li, Y.. Screening high-fluoride and high-arsenic drinking waters and surveying endemic fluorosis and arsenism in Shaanxi province in western China. <i>Water Research</i> . 2006. 40:3015-22	One or more exclusion criteria
L1	Sergeev, M.,Morgia, F.,Lazari, M.,Van Dam, R.. Screening of catalytic activity of transition metal oxides in radiofluorination of tosylated substrates in highly aqueous	One or more exclusion criteria

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L1	Ebrahim, F. M.,Nguyen, T. N.,Shyshkanov, S.,Gladysiak, A.,Favre, P.,Zacharia, A.,Itskos, G.,Dyson, P. J.,Stylianou, K. C.. Selective, Fast-Response, and Regenerable Metal-Organic Framework for Sampling Excess Fluoride Levels in Drinking Water. <i>Journal of the American Chemical Society</i> . 2019. 141:3052-3058	One or more exclusion criteria
L1	Linhares, D. P. S.,Garcia, P. V.,Amaral, L.,Ferreira, T.,Cury, J. A.,Vieira, W.,Rodrigues, A. D. S.. Sensitivity of two biomarkers for biomonitoring exposure to fluoride in children and women: A study in a volcanic area. <i>Chemosphere</i> . 2016. 155:614-620	One or more exclusion criteria
L1	Jahanshahi, M.,Kowsari, E.,Haddadi-Asl, V.,Khoobi, M.,Lee, J. H.,Kadumudi, F. B.,Talebian, S.,Kamaly, N.,Mehrali, M.. Sericin grafted multifunctional curcumin loaded fluorinated graphene oxide nanomedicines with charge switching properties for effective cancer cell targeting. <i>Int J Pharm</i> . 2019. 572:118791	One or more exclusion criteria
L1	Fernando, W. B. N. T.,Nanayakkara, N.,Gunarathne, L.,Chandrajith, R.. Serum and urine fluoride levels in populations of high environmental fluoride exposure with endemic CKDu: a case-control study from Sri Lanka. <i>Environmental geochemistry and health</i> .. 2019. 22:#pages#	One or more exclusion criteria
L1	Ba, Y.,Zhu, J. Y.,Yang, Y. J.,Yu, B.,Huang, H.,Wang, G.,Ren, L. J.,Cheng, X. M.,Cui, L. X.,Zhang, Y. W.. Serum calcitropic hormone levels, and dental fluorosis in children	One or more exclusion criteria

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L1	Koroglu, B. K., Ersoy, I. H., Koroglu, M., Balkarli, A., Ersoy, S., Varol, S., Tamer, M. N.. Serum parathyroid hormone levels in chronic endemic fluorosis. <i>Biological Trace Element Research</i> . 2011. 143:79-86	One or more exclusion criteria
L1	Flueck, W. T., Smith-Flueck, J. A.. Severe dental fluorosis in juvenile deer linked to a recent volcanic eruption in Patagonia. <i>J Wildl Dis</i> . 2013. 49:355-66	One or more exclusion criteria
L1	Fioravanti, A., Tenti, S., Giannitti, C., Fortunati, N. A., Galeazzi, M.. Short- and long-term effects of mud-bath treatment on hand osteoarthritis: A randomized clinical trial. <i>International Journal of Biometeorology</i> . 2014. 58:79-86	One or more exclusion criteria
L1	Yap, H. Y., Fung, S. Y., Ng, S. T., Tan, C. S., Tan, N. H.. Shotgun proteomic analysis of tiger milk mushroom (<i>Lignosus rhinocerotis</i>) and the isolation of a cytotoxic fungal serine protease from its sclerotium. <i>J Ethnopharmacol</i> . 2015. 174:437-51	One or more exclusion criteria
L1	Kim, M., Lee, S. J., Ko, N. R., Kim, D. H., Kim, J. S., Oh, S. J.. Simple and fully automatic production of [¹⁸ F]fluorodeprenyl-D2 using FXFN chemistry module. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2019. 62 (Supplement 1):S332	One or more exclusion criteria
L1	Hyun, J. S., Lee, S. J., Ryu, J. S., Oh, S. J.. Simple and high yield production of 3'-deoxy-3'-[¹⁸ F]fluorothymidine([¹⁸ F]FLT) using SPE method and the minimum precursor amount. <i>Journal of Labelled Compounds and</i>	One or more exclusion criteria

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	<i>Radiopharmaceuticals</i> . 2013. 1):S463	
L1	Nandy, S. K.,Chakraborty, A.,Pawar, Y.,Moghe, S. H.,Rajan, M. G. R.. Simplified and automated synthesis of o-(2-[18f]fluoroethyl)-l-tyrosine ([18f]fet) using a single pot, two-stage procedure and solid-phase extraction purification. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2014. 2):S421	One or more exclusion criteria
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. <i>Molecular Imaging and Biology</i> . 2016. 18 (2 Supplement):S1197-S1198	One or more exclusion criteria
L1	Zhuang, X. M.,Liu, P. X.,Zhang, Y. J.,Li, C. K.,Li, Y.,Wang, J.,Zhou, L.,Zhang, Z. Q.. Simultaneous determination of triptolide and its prodrug MC002 in dog blood by LC-MS/MS and its application in pharmacokinetic studies. <i>J Ethnopharmacol</i> . 2013. 150:131-7	One or more exclusion criteria
L1	Komori, K.,Nada, J.,Nishikawa, M.,Notsu, H.,Tatsuma, T.,Sakai, Y.. Simultaneous evaluation of toxicities using a mammalian cell array chip prepared by photocatalytic lithography. <i>Anal Chim Acta</i> . 2009. 653:222-7	One or more exclusion criteria
L1	Ingallinella, A. M.,Pacini, V. A.,Fernandez, R. G.,Vidoni, R. M.,Sanguinetti, G.. Simultaneous removal of arsenic and fluoride from groundwater by coagulation-adsorption with polyaluminum chloride. <i>Journal of Environmental Science and Health - Part A Toxic/Hazardous Substances and Environmental Engineering</i> . 2011. 46:1288-1296	One or more exclusion criteria
L1	Schofield, R. C.,Mendu, D.,Ramanathan, L. V.,Pessin, M.	One or more exclusion

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	S.,Carlow, D. C.. Simultaneous sensitive quantitation of testosterone and estradiol in serum by LC-MS/MS without derivatization. <i>Clinical Chemistry</i> . 2015. 1):S78-S79	criteria
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L1	Guo, H.,Qian, H.,Idris, N. M.,Zhang, Y.. Singlet oxygen-induced apoptosis of cancer cells using upconversion fluorescent nanoparticles as a carrier of photosensitizer. <i>Nanomedicine</i> . 2010. 6:486-95	One or more exclusion criteria
L1	Kumar, H.,Boban, M.,Tiwari, M.. Skeletal fluorosis causing high cervical myelopathy. <i>J Clin Neurosci</i> . 2009. 16:828-30	One or more exclusion criteria
L1	Izuora, K.,Twombly, J. G.,Whitford, G. M.,Demertzis, J.,Pacifici, R.,Whyte, M. P.. Skeletal fluorosis from brewed tea. <i>J Clin Endocrinol Metab</i> . 2011. 96:2318-24	One or more exclusion criteria
L1	Whyte, M. P.,Totty, W. G.,Lim, V. T.,Whitford, G. M.. Skeletal fluorosis from instant tea. <i>J Bone Miner Res</i> . 2008. 23:759-69	One or more exclusion criteria
L1	Fabreau, G. E.,Bauman, P.,Coakley, A. L.,Johnston, K.,Kennel, K. A.,Gifford, J. L.,Sadrzadeh, H. M.,Whitford, G. M.,Whyte, M. P.,Kline, G. A.. Skeletal fluorosis in a resettled refugee from Kakuma refugee camp. <i>Lancet</i> . 2019. 393:223-225	One or more exclusion criteria
L1	Mohammadi, A. A.,Yousefi, M.,Yaseri, M.,Jalilzadeh, M.,Mahvi, A. H.. Skeletal fluorosis in relation to drinking	One or more exclusion criteria

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	water in rural areas of West Azerbaijan, Iran. <i>Sci Rep.</i> 2017. 7:17300	criteria
L1	Hewavithana, P. B.,Jayawardhane, W. M.,Gamage, R.,Goonaratna, C.. Skeletal fluorosis in Vavuniya District: an observational study. <i>Ceylon Med J.</i> 2018. 63:139-142	One or more exclusion criteria
L1	Kumar, S.,Kakar, A.,Gogia, A.,Byotra, S. P.. Skeletal fluorosis mimicking seronegative spondyloarthropathy: A deceptive presentation. <i>Tropical Doctor.</i> 2011. 41:247-248	One or more exclusion criteria
L1	Crowley, H.. Skeletal fluorosis: As encountered in rural India and its implications for physiotherapists in Asia and Africa. <i>Physiotherapy (United Kingdom).</i> 2011. 1):eS1464	One or more exclusion criteria
L1	McNally, R.,Blakey, K.,Feltbower, R.,Parslow, R.,James, P.,Poza, B. G.,Stiller, C.,Vincent, T.,Norman, P.,McKinney, P.,Murphy, M.,Craft, A.. Small-area analyses of bone cancer in Great Britain, 1980-2005. <i>Pediatric Blood and Cancer.</i> 2010. 55 (5):932-933	One or more exclusion criteria
L1	Karunanidhi, D.,Aravinthasamy, P.,Kumar, D.,Subramani, T.,Roy, P. D.. Sobol sensitivity approach for the appraisal of geomedical health risks associated with oral intake and dermal pathways of groundwater fluoride in a semi-arid region of south India. <i>Ecotoxicol Environ Saf.</i> 2020. 194:110438	One or more exclusion criteria
L1	Frazao, P.,Capel Narvai, P.. Socio-environmental factors associated with dental occlusion in adolescents. <i>American Journal of Orthodontics and Dentofacial Orthopedics.</i> 2006. 129:809-816	One or more exclusion criteria
L1	Bansal, A.,Peng, K. W.,Pandey, M. K.,Suksanpaisan, L.,Russell, S. J.,DeGrado, T. R.. Sodium	One or more exclusion

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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, <i>Carassius auratus</i> . <i>Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology</i> . 2016. 189:54-60	One or more exclusion criteria
L1	Lu, X., Wang, F., Xu, C., Soodvilai, S., Peng, K., Su, J., Zhao, L., Yang, K. T., Feng, Y., Zhou, S. F., Gustafsson, J. Soluble (pro)renin receptor via β -catenin enhances urine concentration capability as a target of liver X receptor. <i>Proc Natl Acad Sci U S A</i> . 2016. 113:E1898-906	One or more exclusion criteria
L1	Firempong, C., Nsiah, K., Awunyo-Vitor, D., Dongsogo, J.. Soluble fluoride levels in drinking water-a major risk factor of dental fluorosis among children in Bongo community of Ghana. <i>Ghana medical journal</i> . 2013. 47:16-23	One or more exclusion criteria
L1	Ghosh, S., Rabha, R., Chowdhury, M., Padhy, P. K.. Source and chemical species characterization of PM(10) and human health risk assessment of semi-urban, urban and industrial areas of West Bengal, India. <i>Chemosphere</i> . 2018. 207:626-636	One or more exclusion criteria
L1	Kumar, R., Mittal, S., Sahoo, P. K., Sahoo, S. K.. Source	One or more exclusion

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L1	Sakizadeh, M.,Ahmadpour, E.,Sharafabadi, F. M.. Spatial analysis of chromium in southwestern part of Iran: probabilistic health risk and multivariate global sensitivity analysis. <i>Environ Geochem Health</i> . 2019. 41:2023-2038	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. <i>Perspectives in Public Health</i> . 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. <i>Chemosphere</i> . 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. <i>Int Dent J</i> .	One or more exclusion criteria

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L1	Yousefi, M.,Asghari, F. B.,Zuccarello, P.,Conti, G. O.,Ejlali, A.,Mohammadi, A. A.,Ferrante, M.. Spatial distribution variation and probabilistic risk assessment of exposure to fluoride in ground water supplies: A case study in an endemic fluorosis region of northwest Iran. <i>Int J Environ Res Public Health</i> . 2019. 16 (4) (no pagination):#pages#	One or more exclusion criteria
L1	Wyss, M. T.,Hofer, S.,Hefti, M.,Bärtschi, E.,Uhlmann, C.,Treyer, V.,Roelcke, U.. Spatial heterogeneity of low-grade gliomas at the capillary level: a PET study on tumor blood flow and amino acid uptake. <i>J Nucl Med</i> . 2007. 48:1047-52	One or more exclusion criteria
L1	Zheng, D.,Liu, Y.,Luo, L.,Shahid, M. Z.,Hou, D.. Spatial variation and health risk assessment of fluoride in drinking water in the Chongqing urban areas, China. <i>Environ Geochem Health</i> . 2020. #volume#:#pages#	One or more exclusion criteria
L1	Fallahzadeh, R. A.,Miri, M.,Taghavi, M.,Gholizadeh, A.,Anbarani, R.,Hosseini-Bandegharaei, A.,Ferrante, M.,Oliveri Conti, G.. Spatial variation and probabilistic risk assessment of exposure to fluoride in drinking water. <i>Food Chem Toxicol</i> . 2018. 113:314-321	One or more exclusion criteria
L1	Sisay, T.,Beyene, A.,Alemayehu, E.. Spatiotemporal variability of drinking water quality and the associated health risks in southwestern towns of Ethiopia. <i>Environ Monit Assess</i> . 2017. 189:569	One or more exclusion criteria
L1	Saifullah, N.,Ahmed, I.,Qayyum, S.,Khan, N.,Hameed Khan, M.. Spirometry changes due to prolonged exposure to high level of fluoride in drinking water. <i>European</i>	One or more exclusion criteria

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L1	de Silva-Sanigorski, A. M.,Waters, E.,Calache, H.,Smith, M.,Gold, L.,Gussy, M.,Scott, A.,Lacy, K.,Virgo-Milton, M.. Splash!: a prospective birth cohort study of the impact of environmental, social and family-level influences on child oral health and obesity related risk factors and outcomes. <i>BMC Public Health. 2011. 11:505</i>	One or more exclusion criteria
L1	Kaisam, J. P.,Kawa, Y. K.,Moiwo, J. P.,Lamboi, U.. State of well-water quality in Kakua Chiefdom, Sierra Leone. <i>Water Science and Technology: Water Supply. 2016. 16:1243-1254</i>	One or more exclusion criteria
L1	Nagaraju, A.,Thejaswi, A.,Sun, L.. Statistical analysis of high fluoride groundwater hydrochemistry in Southern India: Quality assessment and implications for source of fluoride. <i>Environmental Engineering Science. 2016. 33:471-477</i>	One or more exclusion criteria
L1	Usman, A.,Kontagora, N. M.. Statistical process control on production: A case study of some basic chemicals used in pure water production. <i>Pakistan Journal of Nutrition. 2010. 9:387-391</i>	One or more exclusion criteria
L1	Choubisa, S. L.,Choubisa, D.. Status of industrial fluoride pollution and its diverse adverse health effects in man and domestic animals in India. <i>Environmental science and pollution research international. 2016. 23:7244-7254</i>	One or more exclusion criteria
L1	Gryshuk, A.,Chen, Y.,Goswami, L. N.,Pandey, S.,Missert, J. R.,Ohulchanskyy, T.,Potter, W.,Prasad, P. N.,Oseroff, A.,Pandey, R. K.. Structure-activity relationship among	One or more exclusion criteria

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L1	Rathore, S.,Meena, C.,Gonmei, Z.,Dwivedi, S.,Toteja, G. S.,Bala, K.. Study of excess fluoride ingestion and thyroid hormone derangement in relation with different fluoride levels in drinking water among children of Jodhpur District, Rajasthan, India. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences.</i> 2018. 20:327-331	One or more exclusion criteria
L1	Gautam, R.,Bhardwaj, N.,Saini, Y.. Study of fluoride content in groundwater of Nawa Tehsil in Nagaur, Rajasthan. <i>Journal of Environmental Biology.</i> 2011. 32:85-9	One or more exclusion criteria
L1	Sahu, A.,Vaishnav, M. M.. Study of fluoride in ground water around the BALCO, Korba area (India). <i>Journal of Environmental Science & Engineering.</i> 2006. 48:65-8	One or more exclusion criteria
L1	Devesa, V.,Rocha, R.,Montoro, R.,Velez, D.. Study of intestinal transport of F using Caco-2 cell line. <i>Toxicology Letters.</i> 2010. 1):S306	One or more exclusion criteria
L1	Misra, A. K.,Mishra, A.. Study of quaternary aquifers in Ganga Plain, India: focus on groundwater salinity, fluoride and fluorosis. <i>Journal of Hazardous Materials.</i> 2007.	One or more exclusion criteria

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L1	Kumar, T.,Takalkar, A.. Study of the effects of drinking water naturally contaminated with fluorides on the health of children. <i>Biomedical Research</i> . 2010. 21:423-427	One or more exclusion criteria
L1	Liu, G.,Ye, Q.,Chen, W.,Zhao, Z.,Li, L.,Lin, P.. Study of the relationship between the lifestyle of residents residing in fluorosis endemic areas and adult skeletal fluorosis. <i>Environ Toxicol Pharmacol</i> . 2015. 40:326-32	One or more exclusion criteria
L1	Sigchi, S.,Khard, M.,Singh, K. N.,Khare, S.. Study of urinary fluoride estimation among infertility cases in fluorosis endemic area. <i>BJOG: An International Journal of Obstetrics and Gynaecology</i> . 2014. 2):77	One or more exclusion criteria
L1	Nagabhushana, S. R.,Sunilkumar,,Suresh, S.,Sannappa, J.,Srinivasa, E.. Study on activity of radium, radon and physicochemical parameters in ground water and their health hazards around Tumkur industrial area. <i>Journal of Radioanalytical and Nuclear Chemistry</i> . 2020. 323:1393-1403	One or more exclusion criteria
L1	Shashi, A.,Bhardwaj, M.. Study on blood biochemical diagnostic indices for hepatic function biomarkers in endemic skeletal fluorosis. <i>Biol Trace Elem Res</i> . 2011. 143:803-14	One or more exclusion criteria
L1	Liang, Y.,Wang, S. P.,Luo, H.,Zhou, J. H.,Wang, J. W.,Rao, H. X.,Chai, B.. Study on relationship between drinking water endemic fluorosis and urine fluorine in Linyi county, Shanxi province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:193-195	One or more exclusion criteria

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L1	Mitri, E.,Birarda, G.,Vaccari, L.,Kenig, S.,Tormen, M.,Grenci, G.. SU-8 bonding protocol for the fabrication of microfluidic devices dedicated to FTIR microspectroscopy of live cells. <i>Lab Chip</i> . 2014. 14:210-8	One or more exclusion criteria
L1	Baglar, S.. Sub-ablative Er,Cr:YSGG laser irradiation under all-ceramic restorations: effects on demineralization and shear bond strength. <i>Lasers in Medical Science</i> . 2018. 33:41-49	One or more exclusion criteria
L1	Malde, M. K.,Scheidegger, R.,Julshamn, K.,Bader, H. P.. Substance flow analysis: a case study of fluoride exposure through food and beverages in young children living in Ethiopia. <i>Environmental Health Perspectives</i> . 2011. 119:579-84	One or more exclusion criteria
L1	Jung, S.,An, J.,Na, H.,Kim, J.. Surface Energy of Filtration Media Influencing the Filtration Performance against Solid Particles, Oily Aerosol, and Bacterial Aerosol. <i>Polymers (Basel)</i> . 2019. 11:#pages#	One or more exclusion criteria
L1	Tambe, V.,Thakkar, S.,Raval, N.,Sharma, D.,Kalia, K.,Tekade, R. K.. Surface Engineered Dendrimers in siRNA Delivery and Gene Silencing. <i>Curr Pharm Des</i> . 2017. 23:2952-2975	One or more exclusion criteria
L1	Boyer, J. C.,Manseau, M. P.,Murray, J. I.,van Veggel, F. C.. Surface modification of upconverting NaYF ₄ nanoparticles	One or more exclusion criteria

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L1	Hu, L. A.,Wang, Y.,Li, X. L.,Wu, N.. Surveillance analysis of drinking water-born endemic fluorosis in 2009 in Xuchang city, Henan province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:318-320	One or more exclusion criteria
L1	Yu, B.,Liu, Y.,Yuan, C. S.,Kang, J. S.,Huang, H. Q.,Wei, J. J.,Hu, L. A.,Li, A. R.. Surveillance of coal-burning endemic fluorosis prevailing status in Henan province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2009. 28:191-193	One or more exclusion criteria
L1	Sun, D. J.. Surveillance on endemic fluorosis of drinking water type in China: A two-year report of 2003 and 2004. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2007. 26:161-164	One or more exclusion criteria
L1	Wu, J. Q.,Yin, D. M.,Dai, C. F.,Wu, H. Y.,Feng, G. H.,Du, G. X.. Surveillance on water-related endemic fluorosis in Fengshun County Guangdong Province from 1991 to 2005: An outcome analysis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2007. 26:165-167	One or more exclusion criteria
L1	Liu, J. Y.,Liu, H.,Dong, W.,Gao, B.,Liu, Y. Q.,Sun, D. J.. Survey of adult carotid atherosclerosis in water-related endemic fluorosis areas in Heilongjiang province in 2008. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:634-	One or more exclusion criteria

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L1	Chen, P. Z.,Yun, Z. J.,Li, H. X.,Bian, J. C.,Ma, A. H.,Gao, H. X.,Wang, Y. T.,Gao, Jie. Survey of water improvement project to reduce fluoride in Shandong province. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:64-67	One or more exclusion criteria
L1	Bai, S. Y.,Ge, P. F.,Shao, J. Y.,Xu, J. M.,Jia, J. X.,Wang, W. L.,Ren, Y. G.. Survey on water fluoride content and water-improving defluoridation projects in the endemic fluorosis areas of Gansu Province in 2005. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2008. 27:437-440	One or more exclusion criteria
L1	Faidallah, H. M.,Al-Mohammadi, M. M.,Alamry, K. A.,Khan, K. A.. Synthesis and biological evaluation of fluoropyrazolesulfonylurea and thiourea derivatives as possible antidiabetic agents. <i>J Enzyme Inhib Med Chem</i> . 2016. 31:157-163	One or more exclusion criteria
L1	Kim, H.,Choi, J. Y.,Lee, K. H.,Kim, B. T.,Choe, Y. S.. Synthesis and characterization of a difluoroboron complex of fluorine-18 labeled curcumin derivative for beta-amyloid plaque imaging. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2019. 62 (Supplement 1):S390-S391	One or more exclusion criteria
L1	Yu, J.,Mason, R. P.. Synthesis and characterization of novel lacZ gene reporter molecules: detection of beta-	One or more exclusion criteria

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L1	Cai, L.,Liow, J. S.,Morse, C.,Davies, R.,Frankland, M.,Zoghbi, S.,Innis, R.,Pike, V.. Synthesis and evaluation in rats of [¹¹ C] NR2B-Me as a PET radioligand for NR2B subunits in NMDA receptors. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2019. 62 (Supplement 1):S75-S77	One or more exclusion criteria
L1	Attia, K.,Visser, T.,Steven, J.,Slart, R.,Antunes, I.,Van Der Hoek, S.,Elsinga, P.,Heerspink, H.. Synthesis and evaluation of [¹⁸ F] canagliflozin for imaging SGLT-2-transporters in diabetic patients. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2019. 62 (Supplement 1):S27-S29	One or more exclusion criteria
L1	Yoon, K. Y.,Lee, I.,Yang, J.,Lee, J. H.,Choe, Y. S.. Synthesis and evaluation of [F-18] fluoroethyl-RS-0406 as a radioligand for beta-amyloid plaque imaging. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI.</i> 2010. 51:#pages#	One or more exclusion criteria
L1	Lee, I.,Kang, C. M.,Choe, Y. S.,Choi, J. Y.,Lee, K. H.,Kim, B. T.. Synthesis and evaluation of a F-18 labeled reveratrol derivative for beta-amyloid plaque imaging. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2011. 1):S291	One or more exclusion criteria
L1	Mangaiyarkarasi, R.,Chinnathambi, S.,Aruna, P.,Ganesan, S.. Synthesis and formulation of methotrexate (MTX)	One or more exclusion criteria

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	conjugated LaF3:Tb(3+)/chitosan nanoparticles for targeted drug delivery applications. <i>Biomed Pharmacother.</i> 2015. 69:170-8	
L1	Ko, Y. J.,Yun, K. J.,Kang, M. S.,Park, J.,Lee, K. T.,Park, S. B.,Shin, J. H.. Synthesis and in vitro photodynamic activities of water-soluble fluorinated tetrapyridylporphyrins as tumor photosensitizers. <i>Bioorg Med Chem Lett.</i> 2007. 17:2789-94	One or more exclusion criteria
L1	Kumar, P.,Sun, W.,Wuest, M.,Knaus, E. E.,Wiebe, L. I.. Synthesis and initial in vitro and in vivo evaluation of 2'-[¹⁸ F]Fluoro-2'-deoxythymidine ([¹⁸ F]FT) in TK-expressing tumor cells and tissue. <i>Molecular Imaging and Biology.</i> 2010. 2):S1010	One or more exclusion criteria
L1	Izuagie, A. A.,Gitari, W. M.,Gumbo, J. R.. Synthesis and performance evaluation of Al/Fe oxide coated diatomaceous earth in groundwater defluoridation: Towards fluorosis mitigation. <i>Journal of Environmental Science & Health Part A-Toxic/Hazardous Substances & Environmental Engineering.</i> 2016. 51:810-24	One or more exclusion criteria
L1	Selivanova, S. V.,Schubiger, A. P.,Ametamey, S. M.,Stellfeld, T.,Heinrich, T. K.,Meding, J.,Bauser, M.,Hutter, J.. Synthesis and radiofluorination of a high affinity MMP2/MMP9 inhibitor as a potential imaging tracer: Systematic study of diaryliodonium salts precursors. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2011. 1):S5	One or more exclusion criteria
L1	Rodriguez Castillo, A. S.,Guihéneuf, S.,Le Guével, R.,Biard, P. F.,Paquin, L.,Amrane, A.,Couvert, A..	One or more exclusion criteria

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L1	Eskola, O.,Yim, C. B.,Johnson, T.,Bergman, J.,Solin, O.. Synthesis of (18)F-labelled fragmented antibody (18)F Fab. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2019. 62 (Supplement 1):S186-S187	One or more exclusion criteria
L1	Jiang, H.,Pandey, M. K.,DeGrado, T. R.. Synthesis of 18F Tetrafluoroborate via Radiofluorination of BF3. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2015. 1):S255	One or more exclusion criteria
L1	Jiang, H.,Bansal, A.,Pandey, M. K.,Peng, K. W.,Suksanpaisan, L.,Russell, S. J.,DeGrado, T. R.. Synthesis of 18F-Tetrafluoroborate via Radiofluorination of Boron Trifluoride and Evaluation in a Murine C6-Glioma Tumor Model. <i>J Nucl Med.</i> 2016. 57:1454-9	One or more exclusion criteria
L1	Yoshimoto, M.,Honda, N.,Takahashi, K.,Kurihara, H.,Fujii, H.. Synthesis of 4-borono-2- ¹⁸ F-fluoro-phenylalanine using copper-mediated nucleophilic radiofluorination. <i>Journal of Nuclear Medicine. Conference.</i> 2019. 60:#pages#	One or more exclusion criteria
L1	Inkster, J.,Dearling, J.,Snay, E.,Packard, A.. Synthesis of ¹⁸ F-labeled acridinium cations: A new class of potential myocardial perfusion imaging agents. <i>Journal of Nuclear Medicine. Conference.</i> 2019. 60:#pages#	One or more exclusion criteria
L1	Li, M. H.,Shiue, C. Y.,Chang, H. C.,Chu, H. H.. Synthesis of	One or more exclusion

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	<p>[18F]benzamide ([18F]INER-1577) as Histone Deacetylase (HDACs) imaging agent. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI. 2016. 57:#pages#</i></p>	
L1	<p>Rahman, O., Ulin, J., & Langstrom, B. (2010). Synthesis of [18F]fluoroacetate ([18F]FACE) from butyl acetate using commercial platform. Paper presented at the 2010 World Molecular Imaging Congress, Kyoto, Japan.</p>	One or more exclusion criteria
L1	<p>Huang, X., Tian, H.. Synthesis of [¹⁸F]IDO5L: A novel potential PET probe for imaging of IDO-1 expression. <i>Journal of Labelled Compounds and Radiopharmaceuticals. 2015. 1):S197</i></p>	One or more exclusion criteria
L1	<p>Apte, S. D., Chin, F. T., Graves, E. E.. Synthesis of a new PET radiotracer targeting carbonic anhydrase IX. <i>Journal of Labelled Compounds and Radiopharmaceuticals. 2009. 1):S408</i></p>	One or more exclusion criteria
L1	<p>Kniess, T., Kuchar, M., Steinbach, J., Wuest, F.. Synthesis of a potential tyrosine kinase inhibitor by Knoevenagel condensation of oxindole with 4-[18F]fluorobenzaldehyde. <i>Journal of Labelled Compounds and Radiopharmaceuticals. 2009. 1):S182</i></p>	One or more exclusion criteria
L1	<p>Park, J., Kim, H. J., Kim, S., Hur, M. G., Yang, S., Yu, K. H.. Synthesis of F-18 labelled ammonium salts as inhibitor for hEAG1 channels. <i>Journal of Labelled Compounds and Radiopharmaceuticals. 2009. 1):S372</i></p>	One or more exclusion criteria
L1	<p>Rokka, J., Snellman, A., Zona, C., La Ferla, B., Re, F., Masserini, M., Haaparanta, M., Rinne, J., Solin, O.. Synthesis of functionalized [¹⁸F]liposomes for</p>	One or more exclusion criteria

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	preclinical PET imaging in Alzheimer's disease. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2013. 1):S246	
L1	Xiong, L.,Shen, B.,Behera, D.,Gambhir, S. S.,Chin, F. T.,Rao, J.. Synthesis of ligand-functionalized water-soluble [18F]YF3 nanoparticles for PET imaging. <i>Nanoscale</i> . 2013. 5:3253-6	One or more exclusion criteria
L1	Akula, M. R.,Blevins, D. W.,Kabalka, G. W.,Osborne, D.. Synthesis of N-[4-(2'-[¹⁸ F]fluoroethoxybenzoyl)]pyrrolidin-2-one, a potential new brain imaging agent. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2015. 1):S214	One or more exclusion criteria
L1	Mueller, D.,Klette, I.,Kalb, F.,Baum, R.. Synthesis of O-(2-[18F]Fluoroethyl)-L-tyrosine based on a cartridge cleaning method. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI</i> . 2010. 51:#pages#	One or more exclusion criteria
L1	Kumar, N.,Hazari, P. P.,Sony, S.,Swatantra,,Panchal, K. K.,Ramgopal,,Mishra, A. K.. Synthesis of O-(2-[18F]fluoroethyl)-L-Tyrosine based on a cartridge purification method: A simple, fast, and high-yielding automated synthesis. <i>Indian Journal of Nuclear Medicine</i> . 2017. 32 (5 Supplement 1):S45	One or more exclusion criteria
L1	Mueller, D.,Klette, I.,Kalb, F.,Baum, R. P.. Synthesis of O-(2-[18F]fluoroethyl)-L-tyrosine based on a cartridge purification method. <i>Nucl Med Biol</i> . 2011. 38:653-8	One or more exclusion criteria
L1	Yim, C. B.,Mikkola, K.,Nuutila, P.,Solin, O.. Synthesis of pancreatic beta cell-specific [¹⁸ F]fluoro-	One or more exclusion criteria

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	<p>exendin-4 via strain-promoted azadibenzocyclooctyne/azide cycloaddition. <i>EJNMMI Radiopharmacy and Chemistry. Conference: 18th European Symposium on Radiopharmacy and Radiopharmaceuticals. Austria..</i> 2016. 1:#pages#</p>	
L1	<p>Seyedlar, R. M.,Rezvani, M.,Barari, S.,Imani, M.,Nodehi, A.,Atai, M.. Synthesis of plate-like beta-tricalcium phosphate nanoparticles and their efficiency in remineralization of incipient enamel caries. <i>Progress in Biomaterials.</i> 2019. 8:261-276</p>	One or more exclusion criteria
L1	<p>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. <i>Bioorg Med Chem.</i> 2013. 21:8019-32</p>	One or more exclusion criteria
L1	<p>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. <i>Nucleosides Nucleotides Nucleic Acids.</i> 2011. 30:293-315</p>	One or more exclusion criteria
L1	<p>Caballero, J.,Munoz, C.,Alzate-Morales, J. H.,Cunha, S.,Gano, L.,Bergmann, R.,Steinbach, J.,Kniess, T.. Synthesis, in silico, in vitro, and in vivo investigation of 5-[11C]methoxy-substituted sunitinib, a tyrosine kinase inhibitor of VEGFR-2. <i>European Journal of Medicinal Chemistry.</i> 2012. 58:272-80</p>	One or more exclusion criteria

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L1	Yrjölä, S.,Sarparanta, M.,Airaksinen, A. J.,Hytti, M.,Kauppinen, A.,Pasonen-Seppänen, S.,Adinolfi, B.,Nieri, P.,Manera, C.,Keinänen, O.,Poso, A.,Nevalainen, T. J.,Parkkari, T.. Synthesis, in vitro and in vivo evaluation of 1,3,5-triazines as cannabinoid CB2 receptor agonists. <i>Eur J Pharm Sci.</i> 2015. 67:85-96	One or more exclusion criteria
L1	Wang, Y.,McKee, M.,Torbica, A.,Stuckler, D.,Herndon, J. M.. Systematic Literature Review on the Spread of Health-related Misinformation on Social Media Human and Environmental Dangers Posed by Ongoing Global Tropospheric Aerosolized Particulates for Weather Modification. <i>Soc Sci Med.</i> 2019. 240:112552	One or more exclusion criteria
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. <i>Environment International.</i> 2017. 107:163-172	One or more exclusion criteria
L1	Czajka, M.. Systemic effects of fluoridation. <i>Journal of Orthomolecular Medicine.</i> 2012. 27:123-130	One or more exclusion criteria
L1	Indermitte, E.,Karro, E.,Saava, A.. Tap water fluoride levels in Estonia. <i>Fluoride.</i> 2007. 40:244-247	One or more exclusion criteria
L1	Sikorska-Jaroszyńska, M. H. J.,Mielnik-Błaszczak, M.,Krawczyk, D.,Wrobel, R.,Błaszczak, J.. Tea - Natural source of fluoride compounds. <i>Annales Universitatis Mariae Curie-Skłodowska, Sectio DDD: Pharmacia.</i> 2012. 25:247-249	One or more exclusion criteria
L1	Hasan, R.,Talha, M.,Weinstein, R. S.. Tea drinker's fluorosis. <i>Endocrine Reviews. Conference: 99th Annual</i>	One or more exclusion criteria

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L1	Yang, F.,Cui, M.. Technetium-99m labeled phenylquinoxaline derivatives as potential tau-selective imaging probes for diagnosis of Alzheimer's disease. <i>Nuclear Medicine and Biology.</i> 2019. 72-73 (Supplement 1):S56	One or more exclusion criteria
L1	Behnam, B. A.,Ashique, R.,Labiris, R.,Chirakal, R.. Temperature effect on the stereospecificity of nucleophilic fluorination: Formation of [18F]trans-4-fluoro-L-proline during the synthesis of [18F]cis-4-fluoro-L-proline. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2009. 1):S206	One or more exclusion criteria
L1	Azad, B. B.,Ashique, R.,Labiris, N. R.,Chirakal, R.. Temperature effects on the stereospecificity of nucleophilic fluorination: Formation of trans-[¹⁸ F]4-fluoro-l-proline during the synthesis of cis-[¹⁸ F]4-fluoro-l-proline. <i>Journal of Labelled Compounds and Radiopharmaceuticals.</i> 2012. 55:23-28	One or more exclusion criteria
L1	Liu, G.,Sun, Z.,Fu, Z.,Ma, L.,Wang, X.. Temperature sensing and bio-imaging applications based on polyethylenimine/CaF(2) nanoparticles with upconversion fluorescence. <i>Talanta.</i> 2017. 169:181-188	One or more exclusion criteria
L1	Moon, S. H.,Wilks, M.,Takahashi, K.,Han, P.,Ma, C.,Yuan, H.,El Fakhri, G.,Shoup, T.,Normandin, M.. TEMPO as a PET/MR probe of oxidative stress in cell membranes. <i>Journal of Nuclear Medicine. Conference.</i> 2019. 60:#pages#	One or more exclusion criteria

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L1	Ahrari, F.,Eslami, N.,Rajabi, O.,Ghazvini, K.,Barati, S.. The antimicrobial sensitivity of <i>Streptococcus mutans</i> and <i>Streptococcus sanguis</i> to colloidal solutions of different nanoparticles applied as mouthwashes. <i>Dent Res J (Isfahan)</i> . 2015. 12:44-9	One or more exclusion criteria
L1	Leili, M.,Naghibi, A.,Norouzi, H. A.,Khodabakhshi, M.. The assessment of chemical quality of drinking water in Hamadan Province, West of Iran. <i>Journal of Research in Health Sciences</i> . 2015. 15:234-238	One or more exclusion criteria
L1	Angulo, M.,Cuitiño, E.,Molina-Frechero, N.,Emilson, C. G.. The association between the prevalence of dental fluorosis and the socio-economic status and area of residence of 12-year-old students in Uruguay. <i>Acta Odontol Scand</i> . 2020. 78:26-30	One or more exclusion criteria
L1	Allwood-Newhook, L. A.,Chafe, R.,Aslanov, R.,Clarke, J.,Gregory, P.,Gill, N.,Sarkar, A.. The association of type 1 diabetes mellitus and concentrations of drinking water components in Newfoundland and Labrador, Canada. <i>Pediatric Diabetes</i> . 2017. 18 (Supplement 25):64	One or more exclusion criteria
L1	Feng, H. Q.,Shi, Y. X.,Sun, D. J.. The bone metabolism test of rats drinking brick tea liquor before and after defluoridation by Serpentine. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:139-141	One or more exclusion criteria
L1	Skillman, S. M.,Doescher, M. P.,Mouradian, W. E.,Brunson, D. K.. The challenge to delivering oral health services in rural America. <i>Journal of Public Health Dentistry</i> . 2010. 70 Suppl 1:S49-57	One or more exclusion criteria
L1	Mirzabeygi Rad Fard, M.,Yousefi, M.,Soleimani,	One or more exclusion

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	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. <i>Data Brief</i> . 2018. 18:40-46 concentration data of fluoride and health risk assessment in drinking water in the Ardakan city of Yazd province, Iran	criteria
L1	Genovesi, A.,Sachero, E.,Lorenzi, C.. The dental hygienist's role in the laser treatment of the dentine hipersensitivity. [Italian]. <i>Prevenzione e Assistenza Dentale</i> . 2010. 36:32-35	One or more exclusion criteria
L1	Yook, C. M.,Lee, S. J.,Oh, S. J.,Ha, H. J.,Lee, J. J.. The development of new amino acid derivatives using click reaction and simple SPE purification method. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2015. 1):S194	One or more exclusion criteria
L1	Yook, C. M.,Lee, S. J.,Lee, J. J.,Ryu, J. S.,Oh, S. J.. The development of new amino acid derivatives using one pot simultaneous two click reaction. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2013. 1):S365	One or more exclusion criteria
L1	Spittle, B.. The diagnosis of chronic fluoride intoxication including the use of serum and urinary fluoride ion levels and a forearm radiograph in the diagnosis of stage II and III skeletal fluorosis. <i>Fluoride</i> . 2018. 51:3-12	One or more exclusion criteria
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]. <i>Chinese Journal of Endemiology</i> . 2014. 33:315-319	One or more exclusion criteria

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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]. <i>Chinese Journal of Endemiology</i> . 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. <i>J Oral Rehabil</i> . 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. <i>Pediatric Nephrology</i> . 2008. 23:1973-1979	One or more exclusion criteria
L1	Ramesh, M.,Narasimhan, M.,Krishnan, R.,Aruna, R. M.,Kuruvilla, S.. The effect of fluorosis on human teeth under light microscopy: A cross-sectional study. <i>J Oral Maxillofac Pathol</i> . 2017. 21:345-350	One or more exclusion criteria
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. <i>Aust Dent J</i> . 2015. 60:30-7	One or more exclusion criteria
L1	Spittle, B.. The effect of the fluoride ion on reproductive parameters and an estimate of the safe daily dose of fluoride to prevent female infertility and miscarriage, and foetal neurotoxicity. <i>Fluoride</i> . 2017. 50:287-291	One or more exclusion criteria
L1	Nguyen, A.. The effect of various hindered tertiary alcohols on the SN2 radiofluorination of 3'-deoxy-3'-[18 F]fluorothymidine and its in vivo application as a proliferation imaging probe in acute myeloid leukemia.	One or more exclusion criteria

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	<i>Molecular Imaging and Biology</i> . 2017. 19 (1 Supplement 1):S589	
L1	Shim, M. Y.,Parr, C.,Pesti, G. M.. The effects of dietary fluoride on growth and bone mineralization in broiler chicks. <i>Poult Sci</i> . 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. <i>Toxicology Letters</i> . 2009. 190:179-86	One or more exclusion criteria
L1	Spittle, B.. The effects of fluoride on inflammation and cancer. <i>Fluoride</i> . 2019. 52:7-8	One or more exclusion criteria
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. <i>Oper Dent</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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 osteoarthritis. [Russian]. <i>Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury</i> . 2015. 92:48-50	One or more exclusion criteria

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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. <i>American Journal of Gastroenterology</i> . 2015. 1):S731	One or more exclusion criteria
L1	Foth, M.. The increasing relevance of public health research in the last 95 years. <i>Journal of Public Health (Germany)</i> . 2012. 20:209-211	One or more exclusion criteria
L1	Ramadan, A.,Hilmi, Y.. The influence of climate on the determination of the upper permissible fluoride level in potable water in sudan. <i>Fluoride</i> . 2014. 47:170-180	One or more exclusion criteria
L1	Dec, K.,Lukomska, A.,Maciejewska, D.,Jakubczyk, K.,Baranowska-Bosiacka, I.,Chlubek, D.,Wasik, A.,Gutowska, I.. The Influence of Fluorine on the Disturbances of Homeostasis in the Central Nervous System. <i>Biological Trace Element Research</i> . 2017. 177:224-234	One or more exclusion criteria
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. <i>Lasers in Medical Science</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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.	One or more exclusion

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	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]. <i>Chinese Journal of Endemiology</i> . 2011. 30:184-187	criteria
L1	Chachra, D.,Limeback, H.,Willett, T. L.,Grynpas, M. D.. The long-term effects of water fluoridation on the human skeleton. <i>J Dent Res</i> . 2010. 89:1219-23	One or more exclusion criteria
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. <i>FEBS Open Bio</i> . 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. <i>Biomaterials</i> . 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. <i>Arthritis and Rheumatism</i> . 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. <i>Community Dent Health</i> . 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	One or more exclusion criteria

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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 Biosynthesis and Response during Seed Germination and Postgermination Growth in Arabidopsis. <i>Plant Physiology.</i> 2014. 165:1255-1268	One or more exclusion criteria
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. <i>Fluoride.</i> 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. <i>Journal of Hazardous Materials.</i> 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. <i>European Thyroid Journal.</i> 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. <i>J Evid Based Dent Pract.</i> 2006. 6:85-9	One or more exclusion criteria
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	Decay. <i>Pediatric Clinics of North America</i> . 2018. 65:923-940	criteria
L1	Wimalawansa, S. J.. The role of ions, heavy metals, fluoride, and agrochemicals: critical evaluation of potential aetiological factors of chronic kidney disease of multifactorial origin (CKDmfo/CKDu) and recommendations for its eradication. <i>Environ Geochem Health</i> . 2016. 38:639-78	One or more exclusion criteria
L1	Shcherbatykh, I.,Carpenter, D. O.. The role of metals in the etiology of Alzheimer's disease. <i>Journal of Alzheimer's Disease</i> . 2007. 11:191-205	One or more exclusion criteria
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. <i>Supportive Care in Cancer</i> . 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. <i>BMC Plant Biol</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2014. 33:530-533	One or more exclusion criteria
L1	Pepper, I. L.. The soil health-human health nexus. <i>Critical Reviews in Environmental Science and Technology</i> . 2013. 43:2617-2652	One or more exclusion criteria

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L1	Stafford, R.. The spin-echo sequence; K-space. <i>Medical Physics</i> . 2017. 44 (6):3094	One or more exclusion criteria
L1	Shen, Z.,Ning, L.,Wu, R.,Brindle, K.. The technique methods and progress of MR pH imaging. <i>Neuroradiology Journal</i> . 2010. 1):304	One or more exclusion criteria
L1	Whelan, E. M.. The top ten unfounded health scares of the year. <i>MedGenMed Medscape General Medicine</i> . 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]. <i>Zdravniški Vestnik</i> . 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]. <i>Chinese Journal of Clinical Oncology</i> . 2013. 40:621-624+633	One or more exclusion criteria
L1	Taylor, R.,Tolani, N.,Ibbott, G. S.. Thermoluminescence dosimetry measurements of brachytherapy sources in liquid water. <i>Med Phys</i> . 2008. 35:4063-9	One or more exclusion criteria
L1	Talpos, S.. They persisted. <i>Science</i> . 2019. 364:622-626	One or more exclusion criteria
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 and loss of excellent intelligence. <i>Environment</i>	One or more exclusion criteria

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L1	Savchenkov, M. F.,Efimova, N. V.,Manueva, R. S.,Nikolaeva, L. A.,Shin, N. S.. Thyroid gland pathology in children population exposed to the combination of iodine deficiency and fluoride pollution of environment. [Russian]. <i>Gigiena i sanitariia</i> . 2016. 95:1201-1205	One or more exclusion criteria
L1	Abd El Naser Yamamah, G.,Kamel, A. F.,Abd-El Dayem, S.,Hussein, A. S.,Salama, H.. Thyroid volumes and iodine status in Egyptian South Sinai schoolchildren. <i>Archives of Medical Science</i> . 2013. 9:548-54	One or more exclusion criteria
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. <i>Anal Chem</i> . 2019. 91:785-791	One or more exclusion criteria
L1	Chaithra, B.,Sarjan, H. N.,Shivabasavaiah,. Time-dependent effect of ground water fluoride on motility, abnormality and antioxidant status of spermatozoa: An in vitro study. <i>Toxicology and Industrial Health</i> . 2019. 35:368-377	One or more exclusion criteria
L1	Masuda, Y.,Ohji, T.,Kato, K.. Tin oxide nanosheet assembly for hydrophobic/hydrophilic coating and cancer sensing. <i>ACS Appl Mater Interfaces</i> . 2012. 4:1666-74	One or more exclusion criteria
L1	Holmström, K. E.,Berger, U.. Tissue distribution of perfluorinated surfactants in common guillemot (<i>Uria aalge</i>) from the Baltic Sea. <i>Environ Sci Technol</i> . 2008. 42:5879-84	One or more exclusion criteria
L1	Sankhala, S. S.,Harshwal, R.,Paliwal, P.,Agarwal, A.. Toe nails as a biomarker of chronic fluoride exposure to high water fluoride content in areas with endemic	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. <i>Journal of Water & Health</i> . 2010. 8:405-16	One or more exclusion criteria
L1	Clark, D.,Levin, L.. Tooth hypersensitivity treatment trends among dental professionals. <i>Quintessence Int</i> . 2018. 49:147-151	One or more exclusion criteria
L1	Barros, E. L. D.,Pinto, S. C. S.,Borges, A. H.,Tonetto, M. R.,Ellwood, R. P.,Pretty, I.,Bandecca, M. C.. Toothpaste prevents debonded brackets on erosive enamel. <i>Scientific World Journal</i> . 2015. 2015 (no pagination):#pages#	One or more exclusion criteria
L1	Aurlene, N.,Manipal, S.,Rajmohan,,Prabu, D.,Sindhu, R.. Topical fluoride as a panacea for dental caries: A review. <i>Journal of Pharmaceutical Sciences and Research</i> . 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 fluoride, iron, manganese and sulfate. <i>Science of the Total Environment</i> . 2019. 681:497-502	One or more exclusion criteria
L1	Zhu, L.,Zhang, H. H.,Xia, B.,Xu, D. R.. Total fluoride in Guangdong soil profiles, China: Spatial distribution and vertical variation. <i>Environment International</i> . 2007. 33:302-308	One or more exclusion criteria
L1	Paiste, M.,Levine, M.,Bono, J. V.. Total knee arthroplasty in a patient with skeletal fluorosis. <i>Orthopedics</i> . 2012. 35:e1664-7	One or more exclusion criteria

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L1	McCready, R., Dizdarevic, S.. Towards improving the sensitivity of ¹⁸ F bone imaging. <i>Nuclear Medicine Communications</i> . 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. <i>Science of the Total Environment</i> . 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 ¹⁸ F-labeling of Antibodies. <i>Journal of Nuclear Medicine. Conference: Society of Nuclear Medicine and Molecular Imaging Annual Meeting, SNMMI</i> . 2018. 59:#pages#	One or more exclusion criteria
L1	Farooqi, A., Masuda, H., Firdous, N.. Toxic fluoride and arsenic contaminated groundwater in the Lahore and Kasur districts, Punjab, Pakistan and possible contaminant sources. <i>Environmental Pollution</i> . 2007. 145:839-849	One or more exclusion criteria
L1	Choubisa, S. L., Modasiya, V., Bahura, C. K., Sheikh, Z.. Toxicity of fluoride in cattle of the Indian Thar desert, Rajasthan, India. <i>Fluoride</i> . 2012. 45:371-376	One or more exclusion criteria
L1	Grandjean, P., Herz, K. T.. Trace elements as paradigms of developmental neurotoxicants: Lead, methylmercury and arsenic. <i>Journal</i> . 2015. 31:#pages#	One or more exclusion criteria
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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. <i>J Trace Elem Med Biol</i> . 2017. 44:298-306	One or more exclusion criteria
L1	Janka, Z.. Tracing trace elements in mental functions. [Hungarian]. <i>Ideggyogyaszati Szemle</i> . 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. <i>Cancer Research. Conference: 106th Annual Meeting of the American Association for Cancer Research, AACR</i> . 2015. 75:#pages#	One or more exclusion criteria
L1	Chao, W.,Zhang, Y.,Chai, L.,Wang, H.. Transcriptomics provides mechanistic indicators of fluoride toxicology on endochondral ossification in the hind limb of <i>Bufo gargarizans</i> . <i>Aquat Toxicol</i> . 2018. 201:138-150	One or more exclusion criteria
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 NaYF ₄ :Er ³⁺ , Yb ³⁺ up-converting nanoparticles into HeLa cells. <i>Nanotechnology</i> . 2013. 24:235702	One or more exclusion criteria
L1	Wang, P.,Lu, Y.,Wang, T.,Zhu, Z.,Li, Q.,Zhang, Y.,Fu, Y.,Xiao, Y.,Giesy, J. P.. Transport of short-chain perfluoroalkyl acids from concentrated fluoropolymer facilities to the Daling River estuary, China. <i>Environ Sci</i>	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. <i>Clinical Toxicology.</i> 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 burden of bacillary dysentery in China (1991-2000). <i>Bull World Health Organ.</i> 2006. 84:561-8	One or more exclusion criteria
L1	An, N.,Zhu, J.,Ren, L.,Liu, X.,Zhou, T.,Huang, H.,Sun, L.,Ding, Z.,Li, Z.,Cheng, X.,Ba, Y.. Trends of SHBG and ABP levels in male farmers: Influences of environmental fluoride exposure and ESR alpha gene polymorphisms. <i>Ecotoxicology & Environmental Safety.</i> 2019. 172:40-44	One or more exclusion criteria
L1	Loi, E. I. H.,Yeung, L. W. Y.,Taniyasu, S.,Lam, P. K. S.,Kannan, K.,Yamashita, N.. Trophic magnification of poly- and perfluorinated compounds in a subtropical food web. <i>Environmental Science and Technology.</i> 2011. 45:5506-5513	One or more exclusion criteria
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. <i>J Trace Elem Med Biol.</i> 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	One or more exclusion criteria

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L1	Singh, P.,Das, T. K.. Ultrastructural localization of 4-hydroxynonenal adducts in fluoride-exposed cells: Protective role of dietary antioxidants. <i>Fluoride</i> . 2019. 52:49-58	One or more exclusion criteria
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. <i>American Journal of Obstetrics and Gynecology</i> . 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. <i>MEDICC Rev</i> . 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]. <i>Revista Argentina de Endocrinologia y Metabolismo</i> . 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. <i>Macromol Biosci</i> . 2012. 12:1190-9	One or more exclusion criteria

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L1	Diwan, V., Sar, S. K., Biswas, S., Dewangan, R., Baghel, T.. Uranium in ground water of Rajnandgaon District of Central India. <i>Journal of Radioanalytical and Nuclear Chemistry</i> . 2019. 321:293-302	One or more exclusion criteria
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. <i>Environmental Monitoring and Assessment</i> . 2013. 185:2343-2350	One or more exclusion criteria
L1	Liu, H. Y., Chen, J. R., Hung, H. C., Hsiao, S. Y., Huang, S. T., Chen, H. S.. Urinary fluoride concentration in children with disabilities following long-term fluoride tablet ingestion. <i>Res Dev Disabil</i> . 2011. 32:2441-8	One or more exclusion criteria
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. <i>Toxicology Letters</i> . 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. <i>Inorg Chem</i> . 2010. 49:2239-46	One or more exclusion criteria
L1	Samdan, N.. Use of some medicinal plants in ageing. <i>Wiener Klinische Wochenschrift</i> . 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. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2011.	One or more exclusion criteria

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L1	Wang, J.,Holloway, T.,Van Dam, R. M.. Using a microdroplet reactor for rapid, nucleophilic synthesis of [¹⁸ F]FDOPA. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 2019. 62 (Supplement 1):S337-S339	One or more exclusion criteria
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. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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. <i>Journal of Environmental Biology</i> . 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. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 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	One or more exclusion criteria

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L1	De Arcocha Torres, M.,Ortega-Nava, F.,Portilla-Quattrociocchi, H.,Martinez-Rodriguez, I.,Quirce, R.,Medina-Quiroz, P.,Del Carpio-Bellido, L.,Carril, J.. Validation of the Synthesis of (18)F-FNa. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2011. 2):S292	One or more exclusion criteria
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. <i>Critical Reviews in Toxicology</i> . 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. <i>Int J Environ Res Public Health</i> . 2018. 15:#pages#	One or more exclusion criteria
L1	Hari Kumar, K. V. S.,Singh, Y.. Visual vignette. <i>Endocrine Practice</i> . 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. <i>Bioscience Reports</i> . 2018. 38 (4) (no pagination):#pages#	One or more exclusion criteria
L1	Minana, I. V.. Vitamins and trace elements. <i>Pediatrics Integral</i> . 2015. 19:324-336	One or more exclusion criteria
L1	Connett, M. P.. Vulvar Paget's disease: Recovery without surgery following change to very low-fluoride spring and well water. <i>Fluoride</i> . 2007. 40:96-100	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. <i>Nanoscale</i> . 2018. 10:20120-20125	One or more exclusion criteria
L1	Newton, J. N.,Young, N.,Verne, J.,Morris, J.. Water fluoridation and hypothyroidism: results of this study need much more cautious interpretation. <i>J Epidemiol Community Health</i> . 2015. 69:617-8	One or more exclusion criteria
L1	Yeung, C. A.. Water fluoridation could save NHS millions every year. <i>BMJ (Online)</i> . 2014. 348 (no pagination):#pages#	One or more exclusion criteria
L1	Rabb-Waytowich, D.. Water fluoridation in Canada: past and present. <i>J Can Dent Assoc</i> . 2009. 75:451-4	One or more exclusion criteria
L1	Osmunson, B.. Water fluoridation intervention: Dentistry's crown jewel or dark hour?. <i>Fluoride</i> . 2007. 40:214-221	One or more exclusion criteria
L1	Kumar, S.. Water fluoridation, dental fluorosis, bone fluorosis, and skeletal fluorosis among persons in the hojai sub-division, Nagaon District, Assam, India: A quantitative overview. <i>Fluoride</i> . 2012. 45 (3 PART 1):180-181	One or more exclusion criteria
L1	Connett, P.. Water fluoridation--a public health hazard. <i>Int J Occup Environ Health</i> . 2006. 12:88-91	One or more exclusion criteria
L1	Peckham, S.,Awofeso, N.. Water fluoridation: A critical review of the physiological effects of ingested fluoride as a public health intervention. <i>The Scientific World Journal</i> . 2014. 2014 (no pagination):#pages#	One or more exclusion criteria
L1	Amenu, K.,Markemann, A.,Valle Zárate, A.. Water for	One or more exclusion

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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. <i>Ecohealth.</i> 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. <i>Environmental science and pollution research international.</i> 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 Sculpt the Distinctive Shapes and Dynamics of the Tumor-Associated Carbohydrate Tn Antigens: Implications for Their Molecular Recognition. <i>J Am Chem Soc.</i> 2018. 140:9952-9960	One or more exclusion criteria
L1	Varol, E.,Varol, S.. Water-borne fluoride and primary hypertension. <i>Fluoride.</i> 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 eluted from surface pre-reacted glass-ionomer filler promote osteoblastic differentiation of human mesenchymal stem cells. <i>Mol Med Rep.</i> 2018. 17:3448-3454	One or more exclusion criteria

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L1	Ogbu, I. S. I., Okoro, O. I. O., Ugwuja, E. I.. Well waters fluoride in Enugu, Nigeria. <i>International Journal of Occupational and Environmental Medicine</i> . 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. <i>Annals of Allergy, Asthma and Immunology</i> . 2019. 123 (5 Supplement):S67	One or more exclusion criteria
L1	Armfield, J. M.. When public action undermines public health: A critical examination of antifuoridationist literature. <i>Australia and New Zealand Health Policy</i> . 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. <i>Journal of Pediatric Gastroenterology and Nutrition</i> . 2018. 66 (Supplement 2):981	One or more exclusion criteria
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. <i>Sci Rep</i> . 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. <i>Radiology</i> . 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!. <i>Mo Med</i> . 2013. 110:342-3	One or more exclusion criteria

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L1	Huang, C. Q.. X-ray signs of bone and joint among residents of endemic fluorosis area 40 years after improvement of water. [Chinese]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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. <i>Mol Med Rep</i> . 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-controlled hydration for diabetic wound recovery. <i>Journal of Membrane Science</i> . 2020. 598 (no pagination):#pages#	One or more exclusion criteria
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]. <i>Wei sheng yan jiu = Journal of hygiene research</i> . 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]. <i>Fiziol Zh</i> . 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]. <i>Journal of Xi'an</i>	Non-English publication

Level	Bibliography	Reason for Exclusion
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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]. <i>Journal of Xi'an Jiaotong University (Medical Sciences)</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2013. 32:140-145	Non-English publication
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi</i> . 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]. <i>Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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	Non-English publication

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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]. <i>Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology</i> . 2020. 49:168-173	Non-English publication
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Turkish Journal of Medical Sciences</i> . 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]. <i>Chinese</i>	Non-English publication

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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]. <i>Chinese Journal of Endemiology</i> . 2008. 27:371-373	Non-English publication
L2	Gao, Y. H.,Fu, S. B.,Sun, H.,Zhou, L. W.,Yu, J.,Li, Y.,Wang, Y.,Sun, D. J.. Dynamic analysis on bone pathologic change of fluorosis in rats. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2007. 26:18-21	Non-English publication
L2	Gao, Y. H.,Fu, S. B.,Sun, H.,Zhou, L. W.,Yu, J.,Li, Y.,Wang, Y.,Sun, D. J.. Expression of the transforming growth factor-beta superfamily in bone turnover of fluorosis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:374-378	Non-English publication
L2	Gao, Y. H.,Geng, L. B.,Zhao, L. J.,Zhang, L. W.,Wei, W.,Huo, L. L.,Liu, K. K.. Effect of fluoride on bone metabolism in rats. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:613-615	Non-English publication
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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	Non-English publication

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	beta-catenin expression in rat bone tissue]. [Chinese]. <i>Wei sheng yan jiu = Journal of hygiene research</i> . 2011. 40:304-307	
L2	Gutierrez-Salinas, J., Morales-Gonzalez, J. A.. Sodium fluoride ingestion induced oxidative stress in buccal mucosa in rat. [Spanish]. <i>Revista Mexicana de Ciencias Farmaceuticas</i> . 2006. 37:11-22	Non-English publication
L2	Jia, Z., Yu, Y., Yang, X., Wan, W., Xu, W.. Effects of chronic fluorosis on expressions of matrix metalloproteinase-9 mRNA and protein in the osteoclast of bone tissue of rats. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2014. 33:133-137	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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2009. 28:154-156	Non-English publication

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L2	Liu, Y. J.,Gao, Q.,Wu, C. X.,Guan, Z. Z.. Changes of the c-Jun N-terminal kinase in the brains of rats with chronicfluorosis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2010. 29:608-612	Non-English publication
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]. <i>Chinese Journal of Endemiology</i> . 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.. Z. Z.. Changed transcription level of mitochondrial fission and fusion gene loci in cortical neurons of rats with chronic fluorosis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2012. 31:125-129	Non-English publication
L2	Lou, D. D.,Liu, Y. F.,Zhang, K. L.,Yu, Y. N.,Guan, Z. Z.. Changes of reactive oxygen species level and mitochondria fission-fusion in cortical neurons of rats with chronic fluorosis. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2011. 30:256-260	Non-English publication
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 cortical neurons of rats with chronic fluorosis]. [Chinese]. <i>Zhonghua yu fang yi</i>	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]. <i>Chinese Journal of Endemiology. 2013. 32:121-124</i>	Non-English publication
L2	Ma, T. X.,Yu, H. T.,Song, K. Q.. Expression of c-fos and Caspase 8 in cerebral cortex of rats with experimental fluorosis. [Chinese]. <i>Chinese Journal of Endemiology. 2008. 27:131-133</i>	Non-English publication
L2	Mei, M.,Yu, Y. N.,Guo, B.. Effect of fluoride on expression of Runx2 mRNA and protein in bone tissue of rats. [Chinese]. <i>Chinese Journal of Endemiology. 2010. 29:493-495</i>	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]. <i>Chinese Journal of Endemiology. 2010. 29:384-386</i>	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, E.,Hernandez Gil, M. D.. Environmental neurotoxins (IV). Tobacco, alcohol,	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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>National Medical Journal of China</i> . 2012. 92:2357-2361	Non-English publication
L2	Shen, Q., Tian, R., Li, H., Xu, T., Xia, Y.. White matter injury of spinal cord in rats with chronic fluorosis and recovery after defluoriation. [Chinese]. <i>National Medical Journal of China</i> . 2014. 94:1189-1192	Non-English publication
L2	Sun, D. J., Gao, Y. H., Zhou, L. W., Yu, J., Li, Y., Wang, Yu. Effects of sodium fluoride on matrix metal proteinases-13 mRNA and tissue inhibitor of metal protease-1 mRNA in rat	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]. <i>Journal of Jilin University Medicine Edition</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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 musculus incisors in mice. [Chinese]. <i>Journal of Xi'an Jiaotong University (Medical Sciences)</i> . 2011. 32:238-241	Non-English publication
L2	Tao, H.,Wang, L.,Hou, T. Z.,Zhang, L.,Wang, X. R.. Amelogenin gene expression in fluoride-induced musculus incisors of mice. [Chinese]. <i>Journal of Xi'an Jiaotong University (Medical Sciences)</i> . 2010. 31:756-759	Non-English publication
L2	Wang, C. S.,Tang, Y.,Wang, C.. Effect of subchronic exposure to fluoride on mRNA expression of estrogen receptor in female mice. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2013. 32:146-148	Non-English publication
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]. <i>Chinese Journal of Endemiology</i> . 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 kappa beta ligand/receptor activator of nuclear factor kappa beta system proteins of rats with fluorosis and the antagonism of Danlan Xianpeng capsule. [Chinese]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Pathology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2010. 29:124-126	Non-English publication
L2	Xu, H.,Jing, L.,Zhang, J. M.,Li, G. S.. Proteomical analysis of kidney of the fluoride-treated rat. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2008. 27:30-33	Non-English publication
L2	Xu, H.,Zhao, Z. T.,Jing, L.,Li, G. S.. Study on endoplasmic reticulum stress in bone tissue of fluorosis rats. [Chinese]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Journal of Xi'an Jiaotong University (Medical Sciences)</i> . 2008. 29:625-	Non-English publication

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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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2017. 36:327-332	Non-English publication
L2	Yang, Q., Chu, Y., Jiang, W., Li, J., Li, Y., Boo, Y., Chen, F., Li, B., Yang, Y., Guo, Y.. Effects of different doses of sodium fluoride on cartilage lesion and expression of interleukin-6 in Balb/c mice. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2017. 36:408-413	Non-English publication
L2	Yi, G. K., Liu, L., Li, X. Z.. Over-dose fluoride induces the degeneration and ossification of the ligamentum flavum. [Chinese]. <i>Chinese Journal of Tissue Engineering Research</i> . 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 antioxidant and major elements in fluorosis rats. [Chinese]. <i>Chinese Journal of Endemiology</i> . 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	Non-English publication

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L2	Zhang, W. L., Sun, L., Xue, L. J., Wu, Y., Li, G. S.. Study on the relationship of low nutritional calcium with over-load of intracellular calcium in fluorosis mice. [Chinese]. <i>Chinese Journal of Endemiology</i> . 2006. 25:622-624	Non-English publication
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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 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]. <i>Chinese Journal of Endemiology</i> . 2011. 30:137-141	Non-English publication

Level	Bibliography	Reason for Exclusion
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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]. <i>Chinese Journal of Endemiology</i> . 2015. 34:733-738	Non-English publication
L2	Adejumobi, O., Omobowale, T., Oyagbemi, A., Ayenuro, O., Ola-Davies, O., Adedapo, A., Yakubu, M.. Amelioration of sodium fluoride-induced hypertension, cardio-renal oxidative stress and genotoxicity by azadirachta indica through antioxidant and extracellular signal-regulated kinase (erk) 1/2 signal-ling. <i>FASEB Journal. Conference: Experimental Biology</i> . 2017. 31:#pages#	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. <i>Fluoride</i> . 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. <i>Chemosphere</i> . 2015. 135:297-303	Full-text not available
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L2	Khan, I.,Ranga, A.. Sodium fluoride induced toxicity in the kidney of Swiss albino mice and its amelioration by ascorbic acid. <i>International Journal of Pharma and Bio Sciences</i> . 2014. 5:B187-B195	Full-text not available
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L2	Ranjan, R.,Swarup, D.,Patra, R. C.,Varshney, V. P.. Changes in cortisol, oxidative stress indices, and serum biochemistry in fluoride-intoxicated rabbits. <i>Fluoride</i> . 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. <i>Fluoride</i> .	Full-text not available

Level	Bibliography	Reason for Exclusion
	2012. 45 (3 PART 1):198-199	
L2	Shanthakumari, D.,Srinivasalu, S.,Subramanian, S.. Effect of fluoride intoxication on the levels of intestinal antioxidants studied in rats. <i>Methods & Findings in Experimental & Clinical Pharmacology</i> . 2007. 29:93-9	Full-text not available
L2	Shashi, A.,Bhardwaj, M.,Sharma, N.. Pathologic alterations in endocrine pancreatic islet cells during experimental fluuroosis. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences</i> . 2007. 9:977-981	Full-text not available
L2	Shashi, A.,Neeraj, S.,Sharma, N.. Cytotoxic effect of fluoride on rat pancreatic proteins. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences</i> . 2009. 11:349-353	Full-text not available
L2	Shashi, A.,Sharma, N.,Bhardwaj, M.. Fluoride induced DNA damage and apoptosis in rat pancreas. <i>Asian Journal of Microbiology, Biotechnology and Environmental Sciences</i> . 2007. 9:953-957	Full-text not available
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. <i>International Journal of Pharma and Bio Sciences</i> . 2012. 3:B487-B493	Full-text not available
L2	Singh, R.,Srivastava, A. K.,Gangwar, N. K.. Clinico-pathological studies on the co-exposure of cypermethrin and fluoride in experimental rats with ameliorative action of Vitamin E. <i>Veterinary Practitioner</i> . 2017. 18:207-210	Full-text not available
L2	Spittle, B. J.. Fluoride-induced cell ultrastructure changes. <i>Fluoride</i> . 2012. 45 (3 PART 1):201-203	Full-text not available

Level	Bibliography	Reason for Exclusion
L2	Spittle, B.. Fluoride and fertility. <i>Fluoride</i> . 2008. 41:98-100	Full-text not available
L2	Strunecka, A.,Blaylock, R. L.,Strunecky, O.. Fluoride, aluminum, and aluminofluoride complexes in pathogenesis of the autism spectrum disorders: A possible role of immunoexcitotoxicity. <i>Journal of Applied Biomedicine</i> . 2016. 14:171-176	Full-text not available
L2	Sumida, D. H.,Chiba, F. Y.,Colombo, N. H.,Shirakashi, D. J.,Garbin, C. A. S.. The chronic exposure to fluoride inhibits insulin signal in the adipose tissue and causes insulin resistance in rats. <i>Diabetes</i> . 2011. 1):A677	Full-text not available
L2	Tehrani, A.,Morvaridi, A.,Beikzadeh, B.,Hamedani, A. P.,Khadir, F.,Tabari, M. M.. Histological and histometrical studies on the effects of Fluoride on the Femur in rats. <i>Research in Molecular Medicine</i> . 2015. 3:34-38	Full-text not available
L2	Braga, T. M.,Braga, D. N.,Moreno-Carvalho, E.,Bauer, J. O.,Turssi, C. P.. Calcium Pre-Rinse: Effect on permeability of dentin tubules by fluoride rinse. <i>J Clin Exp Dent</i> . 2019. 11:e303-e309	Only dental outcomes
L2	Takei, M.,Sakae, T.,Yoshikawa, M.,Tamura, N.. Effect of fluoride ions on apatite crystal formation in rat hard tissues. <i>Annals of Anatomy</i> . 2007. 189:175-181	Only dental outcomes
L2	Macicek, P.,Krook, L. P.. Fluorosis in horses drinking artificially fluoridated water. <i>Fluoride</i> . 2008. 41:177-183	Only dental outcomes
L2	Mofatto, L. S.,Frozoni, M. R.,do Espírito Santo, A. R.,Guimarães, G. N.,de Souza, A. P.,de Campos Vidal, B.,Line, S. R.. Fluoride effect on the secretory-stage enamel organic extracellular matrix of mice. <i>Connect</i>	Only dental outcomes

Level	Bibliography	Reason for Exclusion
	<i>Tissue Res.</i> 2011. 52:212-7	
L2	Cao, J.,Chen, J.,Wang, J.,Wu, X.,Li, Y.,Xie, L.. Tissue distributions of fluoride and its toxicity in the gills of a freshwater teleost, <i>Cyprinus carpio</i> . <i>Aquatic Toxicology</i> . 2013. 130-131:68-76	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Cardenas-Gonzalez, M.,Jacobco 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. <i>Journal of Applied Toxicology</i> . 2016. 36:309-19	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Casellato, S.,Masiero, L.,Ballarin, L.. Toxicity of fluoride to the freshwater mollusc <i>Dreissena polymorpha</i> : Effects on survival, histology, and antioxidant enzyme activity. <i>Fluoride</i> . 2012. 45:35-46	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Chai, L.,Dong, S.,Zhao, H.,Deng, H.,Wang, H.. Effects of fluoride on development and growth of <i>Rana chensinensis</i> embryos and larvae. <i>Ecotoxicology and Environmental Safety</i> . 2016. 126:129-137	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Chai, L.,Wang, H.,Zhao, H.,Dong, S.. Chronic Effects of Fluoride Exposure on Growth, Metamorphosis, and Skeleton Development in <i>Bufo gargarizans</i> Larvae. <i>Bull Environ Contam Toxicol</i> . 2017. 98:496-501	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Erciyas, K.,Sarikaya, R.. Genotoxic evaluation of sodium	Other exclusion reasons

Level	Bibliography	Reason for Exclusion
	fluoride in the Somatic Mutation and Recombination Test (SMART). <i>Food Chem Toxicol.</i> 2009. 47:2860-2	(route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Feng, P.,Wei, J.,Zhang, Z.. Intervention of selenium on chronic fluorosis-induced injury of blood antioxidant capacity in rats. <i>Biological Trace Element Research.</i> 2011. 144:1024-31	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Gui, C. Z.,Ran, L. Y.,Li, J. P.,Guan, Z. Z.. Changes of learning and memory ability and brain nicotinic receptors of rat offspring with coal burning fluorosis. <i>Neurotoxicology and Teratology.</i> 2010. 32:536-541	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Jianjie, C.,Wenjuan, X.,Jinling, C.,Jie, S.,Ruhui, J.,Meiyan, L.. Fluoride caused thyroid endocrine disruption in male zebrafish (<i>Danio rerio</i>). <i>Aquatic Toxicology.</i> 2016. 171:48-58	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Karademir, B.. Effects of fluoride ingestion on serum levels of the trace minerals Co, Mo, Cr, Mn, and Li in adult male mice. <i>Fluoride.</i> 2010. 43:174-178	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Khanum, Z.,Suleman, S.,Mustanser, A.,Ul Hassan, M. W.,Raees, K.,Kanwal, M. A.,Zia, A.,Ahmad, K. R.. Comparative teratological outcomes of fluoride ions and a fluoridated insecticide (Bifenthrin) in chick embryos.	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-

Level	Bibliography	Reason for Exclusion
	<i>Fluoride</i> . 2019. 52:59-65	mammalian species etc)
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. <i>Toxicology Mechanisms and Methods</i> . 2009. 19:468-475	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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. <i>Toxicology Mechanisms & Methods</i> . 2009. 19:468-75	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Lu, J.,Zheng, J.,Liu, H.,Li, J.,Xu, Q.,Chen, K.. Proteomics analysis of liver samples from puffer fish Takifugu rubripes exposed to excessive fluoride: an insight into molecular response to fluorosis. <i>Journal of Biochemical & Molecular Toxicology</i> . 2010. 24:21-8	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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. <i>Environmental Toxicology and Pharmacology</i> . 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. <i>Neurophysiology</i> . 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..	Other exclusion reasons

Level	Bibliography	Reason for Exclusion
	Protective effects of curcumin against sodium fluoride-induced toxicity in rat kidneys. <i>Biological Trace Element Research</i> . 2012. 145:369-374	(route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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. <i>Fluoride</i> . 2011. 44:147-152	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Nabavi, S. M.,Nabavi, S. F.,Eslami, S.,Moghaddam, A. H.. In vivo protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. <i>Food Chemistry</i> . 2012. 132:931-935	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Nabavi, S. M.,Nabavi, S. F.,Habtemariam, S.,Moghaddam, A. H.,Latifi, A. M.. Ameliorative effects of quercetin on sodium fluoride-induced oxidative stress in rat's kidney. <i>Ren Fail</i> . 2012. 34:901-6	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Nabavi, S. M.,Nabavi, S. F.,Loizzo, M. R.,Sureda, A.,Amani, M. A.,Moghaddam, A. H.. Cytoprotective effect of Silymarin against sodium fluoride-induced oxidative stress in rat erythrocytes. <i>Fluoride</i> . 2012. 45:27-34	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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. <i>Fluoride</i> . 2014. 47:98-108	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-

Level	Bibliography	Reason for Exclusion
		mammalian species etc)
L2	Ranjan, R.,Swarup, D.,Patra, R. C.. Changes in levels of zinc, copper, cobalt, and manganese in soft tissues of fluoride-exposed rabbits. <i>Fluoride</i> . 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. <i>Biological Trace Element Research</i> . 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. <i>Reprod Toxicol</i> . 2006. 22:606-12	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Schieferstein, H.,Betzler, T.,Haller, S.,Cindy, F.,Muller, C.,Ross, T. L.. Total evaluation of a new polar 18F-labeled PEG-click-folate. <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> . 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. <i>Asian Pacific Journal of Tropical Medicine</i> . 2010. 3:136-140	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
L2	Shashi, A.,Sharma, N.,Bhardwaj, M.. Pathological	Other exclusion reasons

Level	Bibliography	Reason for Exclusion
	evaluation of pancreatic exocrine glands in experimental fluorosis. <i>Asian Pacific Journal of Tropical Medicine</i> . 2010. 3:36-40	(route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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 (<i>Acipenser baerii</i>) under laboratory conditions. <i>Chemosphere</i> . 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 <i>Clarias gariepinus</i> . <i>Aquat Toxicol</i> . 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 (<i>Danio rerio</i>) susceptible to bacterial infections. <i>Fish Shellfish Immunol</i> . 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 <i>Ocimum Sanctum</i> in Fluoride induced genotoxicity. <i>International Research Journal of Pharmacy</i> . 2013. 4:160-164	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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	Other exclusion reasons (route of exposure other than drinking water,

Level	Bibliography	Reason for Exclusion
	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. <i>BMC Nephrology</i> . 2020. 21 (1) (no pagination):#pages#	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. <i>Ceylon Med J</i> . 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 <i>Limonia acidissima</i> . <i>Fluoride</i> . 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. <i>Environmental Health and Preventive Medicine</i> . 2012. 17:484-493	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-mammalian species etc)
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. <i>J Hazard Mater</i> . 2018. 346:82-	Other exclusion reasons (route of exposure other than drinking water, mixture exposure, non-

Level	Bibliography	Reason for Exclusion
	92	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. <i>New Zealand Medical Journal</i> . 2015. 128:73-74	Human subjects
L2	Chaitanya, Ncsk,Karunakar, P.,Allam, N. S. J.,Priya, M. H.,Alekhya, B.,Nauseen, S.. A systematic analysis on possibility of water fluoridation causing hypothyroidism. <i>Indian J Dent Res</i> . 2018. 29:358-363	Human subjects
L2	Choi, A. L.,Sun, G.,Zhang, Y.,Grandjean, P.. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. <i>Environ Health Perspect</i> . 2012. 120:1362-8	Human subjects
L2	Yeung, C. A.. A systematic review of the efficacy and safety of fluoridation. <i>Evid Based Dent</i> . 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. <i>PLoS One</i> . 2015. 10:e0126488	Human subjects
L2	Matsui, H.,Morimoto, M.,Horimoto, K.,Nishimura, Y.. Some characteristics of fluoride-induced cell death in rat thymocytes: cytotoxicity of sodium fluoride. <i>Toxicology in Vitro</i> . 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. <i>Bone</i> . 2012. 1):S84	In-vitro models (mammalian cells/ tissues, bacterial cells, plant cells etc.)

Level	Bibliography	Reason for Exclusion
L2	Choubisaa, S. L.. A brief and critical review of endemic hydrofluorosis in Rajasthan, India. <i>Fluoride</i> . 2018. 51:13-33	Non-systematic review
L2	Dhar, V.,Bhatnagar, M.. Physiology and toxicity of fluoride. <i>Indian J Dent Res</i> . 2009. 20:350-5	Non-systematic review
L2	Dharmaratne, R. W.. Exploring the role of excess fluoride in chronic kidney disease: A review. <i>Human and Experimental Toxicology</i> . 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. <i>International Research Journal of Pharmacy</i> . 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. <i>Critical Reviews in Environmental Science and Technology</i> .. 2019. #volume#:#pages#	Non-systematic review
L2	Perumal, E.,Paul, V.,Govindarajan, V.,Panneerselvam, L.. A brief review on experimental fluorosis. <i>Toxicol Lett</i> . 2013. 223:236-51	Non-systematic review
L2	Prystupa, J.. Fluorine - A current literature review. An NRC and ATSDR based review of safety standards for exposure to fluorine and fluorides. <i>Toxicology Mechanisms and Methods</i> . 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. <i>Environ Toxicol Pharmacol</i> . 2017. 56:297-313	Non-systematic review
L2	Strunecka, A.,Strunecky, O.. Chronic Fluoride Exposure and the Risk of Autism Spectrum Disorder. <i>Int J Environ Res Public Health</i> . 2019. 16:#pages#	Non-systematic review

Level	Bibliography	Reason for Exclusion
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. <i>Toxicology Letters</i> . 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. <i>Fluoride</i> . 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. <i>Toxicology Letters</i> . 2012. 1):S4	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Choi, A. L.,Grandjean, P.,Sun, G.,Zhang, Y.. Developmental fluoride neurotoxicity: Choi et al. Respond. <i>Environ Health Perspect</i> . 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). <i>Indian Journal of Endocrinology and Metabolism</i> . 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. <i>Bone</i> . 2011. 48 (6):S284	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Fina, B. L.,Roma, S. M.,Bues, F.,Di Loreto, V. E.. Effect of sodium fluoride (F) on rat growth plate cartilage (GPC).	Commentary/ communication/ editorial/

Level	Bibliography	Reason for Exclusion
	<i>Bone</i> . 2015. 71:258	letter/ conference abstract/ poster/ presentation
L2	Gama-Dominguez, Y., Jacobo-Estrada, T., Lopez-Ventura, D., Moreno-Licon, 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). <i>Toxicology Letters</i> . 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. <i>Free Radical Biology and Medicine</i> . 2010. 1):S221	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
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. <i>Free Radical Biology and Medicine</i> . 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-nitroergic system, cognitive functions and inflammatory markers. <i>Journal of Neurochemistry</i> . 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. <i>Toxicology Letters</i> . 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. <i>Fluoride</i> . 2006. 39:3-10	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation

Level	Bibliography	Reason for Exclusion
L2	Sabour, S.,Ghorbani, Z.. Developmental fluoride neurotoxicity: clinical importance versus statistical significance. <i>Environ Health Perspect.</i> 2013. 121:A70	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Spittle, B.. Fluoride toxicity and donkeys. <i>Fluoride.</i> 2010. 43:4	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation
L2	Spittle, B.. Halting the inertia of indifference: Fluoride and fertility revisited. <i>Fluoride.</i> 2009. 42:159-161	Commentary/ communication/ editorial/ letter/ conference abstract/ poster/ presentation

Section 5. Literature search for in-vitro studies

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 Fluorides, fluorine, flurine, fluoride, fluoridation	Concept 2 Mechanism of action, mode of action, cancer, immunotoxicity, genotoxicity, toxicokinetics, pharmacokinetics

Summary of output

Searched databases	Publications		Level of selection of publications
	All types	Reviews	
Medline	7,939	719	2 concepts (2006-current)
EMBASE	12,185	843	2 concepts (2006-current)
PubMed	5,026	248	2 concepts (2006-current)
TOTAL – before deduplication			
TOTAL³⁰ – after deduplication			

³⁰ Not including bibliographies of examined references/studies/reviews

Bibliographic database search terms and output

Medline Ovid

Concept	#	Medline query	Results
Fluoride	1	exp Fluorides/	36692
	2	exp Fluoridation/	5807
	3	fluorid*.tw.	46854
	4	fluorin*.tw.	24726
	5	flurin*.tw.	6
	6	flurid*.tw.	232
	7	or/1-6	84015
Outcomes	8	Mechanism of action.mp.	70346
	9	(mechanism* adj3 action*).tw.	127638
	10	mode of action.mp.	31469
	11	(mode* adj3 action*).tw.	45237
	12	exp Adverse Outcome Pathways/	74
	13	exp Toxicity Tests/	110616
	14	(toxic* adj3 test*).tw.	16946
	15	exp Animal Testing Alternatives/	3293
	16	(toxic* adj3 test*).tw.	16946
	17	Molecular initiating events.mp.	84
	18	exp In Vitro Techniques/	590172
	19	in vitro testing.mp.	3264
	20	in vitro test*.mp.	12152
	21	Structure-Activity Relationship/	174437
	22	structure activity relationship*.tw.	35238
	23	exp Pharmacokinetics/	305321
	24	pharmacokinetic*.tw.	156167
	25	toxicokinetics/	564
	26	toxicokinetic*.tw.	3957
	27	exp Neoplasms/	3272969
	28	neoplas*.tw.	256019

Concept	#	Medline query	Results
	29	cancer*.tw.	1708153
	30	malignan*.tw.	557197
	31	tumor*.tw.	1399337
	32	tumour*.tw.	264854
	33	sarcoma*.tw.	93788
	34	carcinoma*.tw.	641589
	35	Mutagens/	29170
	36	Mutagenicity Tests/	17114
	37	mutagen*.tw.	112688
	38	Mutation/	419475
	39	mutation*.tw.	619079
	40	genotox*.tw.	33102
	41	Toxicogenetics/	846
	42	toxicogenetic*.tw.	96
	43	micronucle*.tw.	14773
	44	electrophil*.tw.	15711
	45	Carcinogenesis/	12664
	46	carcinogen*.tw.	137554
	47	DNA Damage/	65176
	48	(dna adj3 damage*).tw.	82615
	49	Oxidative Stress/	128743
	50	oxidative stress.tw.	175319
	51	epigenetic*.tw.	76064
	52	Genomic Instability/	7624
	53	(gen* adj3 instabilit*).tw.	15934
	54	DNA Repair/	48704
	55	(dna adj3 repair).tw.	57731
	56	chronic inflamm*.tw.	59714
	57	immortaliz*.tw.	20410
	58	Immunosuppressive Agents/	94418

Concept	#	Medline query	Results
	59	(immunosuppressi* adj3 agent*).tw.	11153
	60	receptor mediated effect*.tw.	1045
	61	Cell Transformation, Neoplastic/	60040
	62	(cell* adj3 transformation*).tw.	21256
	63	Cell Proliferation/	218511
	64	(cell* adj3 proliferation*).tw.	271003
	65	Cell Death/	45588
	66	(cell* adj3 death*).tw.	168258
	67	SAR.tw.	16656
	68	ADME.tw.	2503
	69	or/8-68	6666866
Fluoride + outcomes	70	7 and 69	16345
2006 - current	71	limit 70 to yr="2006 -Current"	7939
Rev/ SR /MA /CR	72	limit 71 to (meta analysis or "review" or "scientific integrity review" or "systematic review" or systematic reviews as topic)	719

EMBASE

Concept	#	EMBASE query	Results
Fluoride	1	exp fluoride/	35,467
	2	exp fluoridation/	6,247
	3	fluorid*.tw.	55,347
	4	flurid*.tw.	209
	5	fluorin*.tw.	29,221
	6	flurin*.tw.	21
	7	or/1-6	91,724
Outcomes	8	exp adverse outcome pathway/	303
	9	exp toxicity testing/	45,203
	10	exp animal testing alternative/	2,528
	11	exp in vitro study/	5,967,650
	12	exp structure activity relation/	192,917
	13	exp pharmacokinetics/	728,239
	14	toxicokinetics/	11,781
	15	exp neoplasm/	4,776,218
	16	exp malignant neoplasm/	3,581,546
	17	neoplas*.tw.	366,974
	18	cancer*.tw.	2,479,130
	19	malignan*.tw.	833,939
	20	carcino*.tw.	1,089,354
	21	sarco*.tw.	240,714
	22	tumor*.tw.	1,962,166
	23	tumour*.tw.	426,370
	24	exp mutagenic agent/	19,000
	25	(mutagen* adj3 agen*).tw.	1,431
	26	exp mutagen testing/	30,874
	27	(mutagen* adj3 test*).tw.	4,565
	28	exp mutation/	1,172,173
	29	mutation*.tw.	832,123

Concept	#	EMBASE query	Results
	30	exp gene mutation/	721,611
	31	(gene* adj3 mutation*).tw.	156,767
	32	exp genotoxicity/	32,745
	33	exp genotoxicity assay/	8,698
	34	genotox*.tw.	40,902
	35	exp toxicogenetics/	1,032
	36	toxicogen*.tw.	2,168
	37	carcinogenesis/	182,175
	38	(cancer* adj3 induction).tw.	5,533
	39	(cancer* adj3 theor*).tw.	1,909
	40	cancerogen.tw.	93
	41	neoplasmoden.tw.	-
	42	oncogen.tw.	405
	43	tumorigen.tw.	96
	44	tumourigen.tw.	3
	45	(tumor* adj3 formation).tw.	23,293
	46	(tumour* adj3 formation).tw.	3,400
	47	(tumor* adj3 genesis).tw.	1,164
	48	(tumour* adj3 genesis).tw.	291
	49	(tumor* adj3 induction).tw.	9,484
	50	(tumour* adj3 induction).tw.	1,702
	51	exp micronucleus/	8,775
	52	micronucle*.tw.	17,680
	53	exp DNA damage/	143,856
	54	(dna adj3 damag*).tw.	110,172
	55	(dna adj3 break*).tw.	33,127
	56	(dna adj3 lesion*).tw.	11,399
	57	(dna adj3 fragment*).tw.	62,587
	58	exp DNA repair/	93,230
	59	(dna adj3 repair*).tw.	76,069

Concept	#	EMBASE query	Results
	60	(gen* adj3 repair*).tw.	19,933
	61	exp chromosome aberration/	204,053
	62	(chromosom* adj3 aberration*).tw.	28,335
	63	(chromosom* adj3 anomal*).tw.	6,740
	64	(chromosom* adj3 abnormal*).tw.	31,791
	65	(chromosom* adj3 defect*).tw.	3,580
	66	(chromosom* adj3 error*).tw.	1,009
	67	exp oxidative stress/	280,685
	68	oxidative stress*.tw.	233,273
	69	exp electrophilic stress/	288
	70	electrophil* stress*.tw.	262
	71	exp epigenetics/	72,239
	72	epigenetic*.tw.	106,194
	73	exp cell transformation/	132,325
	74	(cell* adj3 transformation*).tw.	26,817
	75	exp cell proliferation/	502,056
	76	(cell* adj3 proliferat*).tw.	414,852
	77	exp cell death/	148,899
	78	(cell* adj3 death).tw.	217,775
	79	(cell* adj3 necrosis).tw.	17,903
	80	(cell* adj3 aging).tw.	9,410
	81	(cell* adj3 degeneration).tw.	11,723
	82	(cell* adj3 survival).tw.	107,618
	83	(gene* adj3 transformation*).tw.	7,356
	84	genomic instability/	18,837
	85	gen* instabilit*.tw.	18,896
	86	genetic stability/	10,184
	87	(gen* adj3 stabilit*).tw.	17,142
	88	(gen* adj3 damag*).tw.	18,571
	89	exp chronic inflammation/	33,613

Concept	#	EMBASE query	Results
	90	chronic inflammat*.tw.	93,597
	91	or/8-90	
			12,062,946
Fluoride + outcomes	92	7 and 91	25,744
2006 - current	93	limit 92 to yr="2006 -Current"	12,185
Reviews only	94	limit 93 to Review	843

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] 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*	

Concept	#	Pubmed query	Results
		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]) 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*	

Concept	#	Pubmed query	Results
		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 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])	12181

Concept	#	Pubmed query	Results
		<p>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* 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*</p>	

Concept	#	Pubmed query	Results
		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 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	5026

Concept	#	Pubmed query	Results
		<p> anomalous[Text Word]) OR chromosome abnormality[MeSH Terms]) OR chromosomal abnormal*[Text Word]) OR chromosome defective micronucleus[MeSH Terms]) OR chromosomal defect*[Text Word]) OR chromosomal 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* necrosis*[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])) AND ((((("meta analysis"[Publication Type]) OR "systematic review"[Publication Type]) OR "review"[Publication Type]) OR "scientific integrity </p>	

Concept	#	Pubmed query	Results
		review"[Publication Type]) OR "guideline"[Publication Type])	

Section 6. Weight of evidence using Bradford Hill considerations for causality³¹

Reducing IQ scores

Strength of association

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Feng 2022 ^[4]	High fluoride group (HFG) Change in IQ score per 1.0 mg/L increase in UFcr level: $\beta = -2.502$ (95% CI: -4.411, -0.593)	P=0.010	Positive	Children
Goodman 2022 ^[6]	Changes in cognitive score 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) PIQ: B=-2.63 (95% CI: -3.87, -1.40) VIQ: B=-1.29 (95% CI: -2.60, 0.01);	P=0.002 P<0.001 P=0.053	Positive	Children
Ibarluzea 2022 ^[8]	Changes in cognitive score per unit (mg/g) increase in maternal creatinine-adjusted urinary fluoride (MUFcr), β (95% CI) <u>Bayley Mental Development Index (MDI)</u> <i>Both trimesters MUFcr</i> • All: 1.48 (-4.2, 7.16) • Boys: 3.84 (-5.04, 12.72) • Girls: 0.75 (-6.92, 8.43) <u>McCarthy, verbal</u> <i>Both trimesters MUFcr</i>	 P<0.05	Positive	Children

³¹ : Includes data from RSI-identified studies only.

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> All: 13.86 (3.91, 23.82) Boys: 13.38 (2.81, 23.95) Girls: -1.31 (-9.35, 6.74) 			
	<u>McCarthy, performance</u> <i>Both trimesters MUFcr</i> <ul style="list-style-type: none"> All: 5.86 (0.32, 11.39) Boys: 12.24 (2.87, 21.61) Girls: 2.03 (-4.77, 8.83) 	P<0.05		
	<u>McCarthy, numeric</u> <i>Both trimesters MUFcr</i> <ul style="list-style-type: none"> All: 6.22 (0.65, 11.79) Boys: 11.09 (1.79, 20.4) Girls: 3.03 (-3.96, 10.03) 	P<0.05		
	<u>McCarthy, memory</u> <i>Both trimesters MUFcr</i> <ul style="list-style-type: none"> All: 11.63 (2.62, 20.63) Boys: 11.3 (1.90, 20.7) Girls: -2.12 (-9.32, 5.09) 	P<0.05		
	<u>McCarthy, general cognitive</u> <i>Both trimesters MUFcr</i> <ul style="list-style-type: none"> All: 15.4 (6.32, 24.48) Boys: 15.03 (5.3, 24.75) Girls: -0.02 (-7.16, 7.12) 	P<0.01		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
<p>Changes in cognitive score per unit (mg/g) increase in MUFcr, β (95% CI), stratified by fluoridated and non-fluoridated zone</p>				
<p><u>Bayley Mental Development Index (MDI)</u></p>				
<p><i>Both trimesters MUFcr</i></p>				
<ul style="list-style-type: none"> • Both zones/non-fluoridated: -0.52 (-7, 5.95) • No significant interaction by zone 				
<hr/> <p><u>McCarthy, verbal</u></p>				
<ul style="list-style-type: none"> • P<0.01 				
<p><i>Both trimesters MUFcr</i></p>				
<ul style="list-style-type: none"> • Both zones/non-fluoridated: 15.58 (3.71, 27.45) • Fluoridated zone: -2.4 (-11.17, 6.37) 				
<hr/> <p><u>McCarthy, performance</u></p>				
<p>P<0.05</p>				
<p><i>Both trimesters MUFcr</i></p>				
<ul style="list-style-type: none"> • Both zones/non-fluoridated: 7.82 (1.58, 14.07) • Fluoridated zone: not reported 				
<hr/> <p><u>McCarthy, numeric</u></p>				
<p><i>Both trimesters MUFcr</i></p>				
<ul style="list-style-type: none"> • Both zones/non-fluoridated: 4.08 (-2.21, 10.36) • No significant interaction by zone 				
<hr/> <p><u>McCarthy, memory</u></p>				
<p><i>Both trimesters MUFcr</i></p>				
<ul style="list-style-type: none"> • Both zones/non-fluoridated: 2.71 (-3.77, 9.18) • No significant interaction by zone 				
<hr/> <p><u>McCarthy, general cognitive</u></p>				
<p>P<0.01</p>				
<p><i>Both trimesters MUFcr</i></p>				

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> Both zones/non-fluoridated: 15.46 (4.55, 26.36) Fluoridated zone: 1.96 (-6.09, 10.02) 			
Saeed 2022 [13]	<p>Non-verbal intelligence quotient (IQ) IQ score</p> <p>Control group: 80.25–127.75; mean 100.93 (SD 13.1) Exposed group: 63.97–127.31; mean 97.26 (SD 15.39)</p>	P=0.233	Positive	Children/adolescents
	<p><u>Correlation analysis</u></p> <p>Water fluoride and urinary fluoride: R²=0.224</p>	P=0.006		
	<p>Water fluoride and IQ score: R²=-0.034</p>	P=0.683		
	<p>Urinary fluoride and IQ score: R²=-0.655</p>	P=0.000		
	<p><u>Intelligence level vs mean (SD) water fluoride (WF), urinary fluoride (UF)</u></p>			
	<p>Superior (IQ score ≥130): no participants with this level</p>			
	<p>Above average (IQ score 120-129)</p>			
	<ul style="list-style-type: none"> WF: 1.96±2.77 mg/L UF: 0.54±0.59 mg/L 			
	<p>High Average (IQ score 111-119)</p>			
	<ul style="list-style-type: none"> WF: 4.60±4.40 mg/L UF: 1.20±0.80 mg/L 			
	<p>Average (IQ score 90-100)</p>			
	<ul style="list-style-type: none"> WF: 4.3±3.99 mg/L UF: 1.99±1.28 mg/L 			

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<p>Low average (IQ score 80-89)</p> <ul style="list-style-type: none"> • WF: 3.84±3.63 mg/L • UF: 3.61±2.84 mg/L <p>Borderline (IQ score 70-79)</p> <ul style="list-style-type: none"> • WF: 6.19±4.59 mg/L • UF: 7.13±2.62 mg/L <p>Retarded (IQ score <70)</p> <ul style="list-style-type: none"> • WF: 4.92±3.46 mg/L UF: 8.10±5.84 mg/L 			
Farmus 2021 [21]	<p>Change (95% CI) in age-normed in FSIQ scores per unit increase in standardized fluoride exposure</p> <p><u>Males</u></p> <ul style="list-style-type: none"> • MUF: -1.86 (-3.22, -0.49) • IFI: -0.01 (-1.67, 1.65) CUF: 0.07 (-1.66, 1.80) 	P=0.012	Positive	Children
	<p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: -0.23 (-2.06, 1.60) • IFI: -0.72 (-2.34, 0.89) CUF: -0.41 (-2.07, 1.24) 	P=0.77		
	<p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: -1.28 (-2.37, -0.18) • IFI: -0.38 (-1.53, 0.78) CUF: -0.18 (-1.38, 1.02) 	P=-0.23		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	Change (95% CI) in age-normed in PIQ scores per unit increase in standardized fluoride exposure	P=0.01		
	<u>Males</u>			
	• MUF: -3.01			
	• IFI: -1.45 (-3.40, 0.49)			
	CUF: -1.49 (-3.50, 0.53)			
	<u>Females</u>	P=0.01		
	• MUF: -1.18 (-3.32, 0.96)			
	• IFI: -2.71 (-4.59, -0.83)			
	CUF: -1.53 (-3.45, 0.39)			
	<u>Overall</u>	P=<0.001		
	• MUF: -2.36 (-3.63, -1.08)			
	• IFI: -2.11 (-3.45, -0.76)			
	CUF: -1.51 (-2.90, -0.12)			
	Change (95% CI) in age-normed in VIQ scores per unit increase in standardized fluoride exposure	P=0.12		
	<u>Males</u>			
	• MUF: -0.25 (-1.57, 1.07)			
	• IFI: 1.22 (-0.39, 2.83)			
	CUF: 1.61 (-0.06, 3.29)			
	<u>Females</u>	P=0.30		
	• MUF: 0.87 (-0.91, 2.64)			
	• IFI: 1.31 (-0.25, 2.87)			
	CUF: 0.63 (-0.98, 2.23)			
	<u>Overall</u>	P=0.04		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> • MUF: 0.15 (-0.91, 1.20) • IFI: 1.27 (0.15, 2.39) CUF: 1.10 (-0.06, 2.26) 			
	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	P=0.12		
	<u>Males</u>			
	<ul style="list-style-type: none"> • MUF: -2.48 (-4.30, -0.66) • IFI: -0.01 (-1.25, 1.24) CUF: 0.09 (-2.10, 2.28) 			
	<u>Females</u>	P=0.77		
	<ul style="list-style-type: none"> • MUF: -0.31 (-2.76, 2.14) • IFI: -0.54 (-1.75, 0.66) CUF: -0.52 (-2.62, 1.58) 			
	<u>Overall</u>	P=0.23		
	<ul style="list-style-type: none"> • MUF: -1.71 (-3.17, -0.24) • IFI: -0.28 (-1.15, 0.58) CUF: -0.23 (-1.75, 1.29) 			
	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	P=0.01		
	<u>Males</u>			
	<ul style="list-style-type: none"> • MUF: -4.02 (-6.15, -1.89) • IFI: -1.09 (-2.54, 0.37) CUF: -1.89 (-4.44, 0.67) 			
	<u>Females</u>	P=0.01		
	<ul style="list-style-type: none"> • MUF: -1.58 (-4.43, 1.28) 			

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> • IFI: -2.03 (-3.43, -0.63) CUF: -1.94 (-4.37, 0.50) 			
	<p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: -3.15 (-4.85, -1.44) • IFI: -1.58 (-2.59, -0.57) CUF: -1.91 (-3.68, -0.15) 	P=<0.001		
	<p>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</p>	P=0.12		
	<p><u>Males</u></p> <ul style="list-style-type: none"> • MUF: -0.34 (-2.10, 1.43) • IFI: 0.92 (-0.29, 2.12) CUF: 2.05 (-0.08, 4.16) 			
	<p><u>Females</u></p> <ul style="list-style-type: none"> • MUF: 1.16 (-1.22, 3.53) • IFI: 0.98 (-0.19, 2.15) CUF: 0.79 (-1.24, 2.82) 	P=0.30		
	<p><u>Overall</u></p> <ul style="list-style-type: none"> • MUF: 0.20 (-1.22, 1.61) • IFI: 0.95 (0.11, 1.79) CUF: 1.39 (-0.08, 2.86) 	P=0.04		
	<p>Sensitivity analysis where influential mother-child dyads were removed was conducted</p> <ul style="list-style-type: none"> • Association of MUF and FSIQ in boys became weaker and not statistically significant • No change in status of statistical significance for other 			

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
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associations tested

Wang 2021 [32]	<p><u><i>IQ, Linear regression</i></u></p> <ul style="list-style-type: none"> Water fluoride (mg/L): IQ scores, β (95% CI), Q1 (≤ 0.30): Reference: <ul style="list-style-type: none"> Q2 (0.30–1.00) <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> All: -2.77 (-5.44, -0.10) Boys: -4.45 (-8.41, -0.50) Girls: -1.72 (-5.91, 2.47) Q4 (> 1.60) <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> Q2 (0.20–0.48) <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> All: -3.02 (-5.71, -0.33) Boys: -3.54 (-7.60, 0.52) 		Positive	Children
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Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	Girls: -1.86 (-6.01, 2.29) o Q4 (> 0.90) All: -4.49 (-7.21, -1.77) Boys: -6.09 (-10.29, -1.90) Girls: -5.98 (-9.99, -1.96) <u><i>IQ, Logistic regression</i></u> • Water fluoride (mg/L) and IQ scores [OR (95% CI)] o Superior and above (≥120): 0.69 (0.54, 0.90) o High normal (110-119): 0.86 (0.70, 1.06) o Normal (90-109): 1 (control) o Dull normal and below (≤89): 1.42 (1.08, 1.88) • Urinary fluoride (mg/L) and IQ scores [OR (95% CI)] o Superior and above (≥120): 0.67 (0.46, 0.97) o High normal (110-119): 0.90 (0.68, 1.18) o Normal (90-109): 1 (control) Dull normal and below (≤89): 1.39 (0.97, 2.00)			
Similar results were obtained with sensitivity analyses for the association between fluoride exposure and IQ reduction				
Cui 2020 [37]	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	<i>Non-significant association</i>	Children/ adolescents
Soto-Barreras 2019 [62]	Mean (±SD) water fluoride levels (mg/L) by intellectual grade categories • Grade I: 1.48 ± 1.13	0.645	<i>No association</i>	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> • Grade II: 1.05 ± 1.06 • Grade III: 1.04 ± 1.06 • Grade IV: 0.97 ± 1.10 • Grade V: 0.79 ± 1.17 			
	<hr/> Mean (±SD) urinary fluoride levels (mg/L) by intellectual grade categories	0.559		
	<ul style="list-style-type: none"> • 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 			
	<hr/> Mean (±SD) exposure dose/daily intake by intellectual grade categories	0.389		
	<ul style="list-style-type: none"> • 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 			
Arulkumar 2017 [78]	Serum level of AChE (U/l) <ul style="list-style-type: none"> • Controls: 6.29 ± 0.68 • Mild: 4.64 ± 0.54 • Moderate: 4.11 ± 0.4 • Severe: 3.78 ± 0.35 	P< 0.001	Possibly positive	Adults (fluorosis patients)
	<hr/> Serum level of ATPase/Na+ K+ ATPase	P< 0.001		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> • Controls: 2.41 ± 0.34 • Mild: 2.56 ± 0.31 • Moderate: 2.64 ± 0.29 • Severe: 2.87 ± 0.4 			
Bashash 2017 ^[79]	Change in outcome per 0.5 mg/L increase in maternal urinary fluoride levels <ul style="list-style-type: none"> ○ <i>GCI</i>: $\beta = -3.15 (-5.42, -0.87)$ ○ <i>IQ</i>: $\beta = -2.50 (-4.12, -0.59)$ <hr/> Change in outcome per 0.5 mg/L increase in child urinary fluoride levels <ul style="list-style-type: none"> ○ <i>IQ</i> – Without adjustment of maternal urinary fluoride levels: $\beta = -0.89 (-2.63, 0.85)$ ○ <i>IQ</i> – With adjustment of maternal urinary fluoride levels $\beta = -0.77 (-2.53, 0.99)$ 	<p>$p = 0.01$</p> <hr/> <p>$p = 0.01$</p> <p><i>Non-significant</i></p> <p><i>Non-significant</i></p>	Positive	Children/ adolescents
Yani 2021 ^[33]	IQ <ul style="list-style-type: none"> • High-fluoride area: <ul style="list-style-type: none"> ○ Low: 17 (28.3%) ○ High: 43 (71.7%) • Low-fluoride area: <ul style="list-style-type: none"> ○ Low: 0 (0%) ○ High: 40 (100%) IQ and Dental fluorosis <ul style="list-style-type: none"> • Dental fluorosis: <ul style="list-style-type: none"> ○ Low: 15 (37.5%) 		Positive	Children

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Yu 2021 [34]	<ul style="list-style-type: none"> ○ High: 25 (62.5%) ● No dental fluorosis: <ul style="list-style-type: none"> ○ Low: 2 (3.3%) ○ High: 28 (96.6%) <hr/> <p><u>Does-response relationships of IQ scores with fluoride exposures (β and 95% CI for every 0.50 mg/L increment of water fluoride or urinary fluoride)</u></p> <ul style="list-style-type: none"> ● Water fluoride (mg/L) <ul style="list-style-type: none"> ○ 0.20-3.40 <ul style="list-style-type: none"> Crude: -1.24 (-1.48, -0.99) Adjusted: -1.16 (-1.41, -0.91) ○ 3.40-3.90 <ul style="list-style-type: none"> Crude: -5.36 (-8.54, -2.18) Adjusted: -4.21 (-7.54, -0.87) ● Urinary fluoride (mg/L) <ul style="list-style-type: none"> ○ 0.01-1.60 <ul style="list-style-type: none"> Crude: 0.96 (0.29, 1.63) Adjusted: 1.01 (0.34, 1.68) ○ 1.60-2.50 <ul style="list-style-type: none"> Crude: -5.08 (-6.94, -3.22) Adjusted: -5.23 (-7.07, -3.39) ○ 2.50-5.54 <ul style="list-style-type: none"> Crude: -0.50 (-1.13, 0.14) Adjusted: -0.34 (-0.98, 0.30) 	Positive	Children	
Zhao 2021 [35]	<u>Associations between UF and IQ scores</u>	Positive	Children	

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> Overall: Log_UF were inversely linear associated with IQ score ($P < 0.05$) in both crude model and adjusted model β (95% CI): <ul style="list-style-type: none"> 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; $p=0.006$) 			
Cui 2018 [67]	<p>Change (95% CI) in IQ score per log-unit increase in urinary fluoride among all participants and by subgroups</p> <p><u>Overall (N = 323)</u></p> <p>$\beta = -2.47 (-4.93, - 0.01)$, $p = 0.049$</p> <p>[Bootstrapped estimate: 95%CI = -4.97, 0.03]</p> <hr/> <p><u>DRD2 SNP of CC or CT (N = 279)</u></p> <p>$\beta = - 1.59 (- 4.24, 1.05)$</p> <p>[Bootstrapped estimate: 95%CI= -4.14, 0.95]</p> <hr/> <p><u>DRD2 SNP of TT (N = 44)</u></p> <p>$\beta = -12.31 (-18.69, -5.94)$, $p < 0.001$</p> <p>[Bootstrapped estimate: 95%CI= -19.66, -4.96]</p> <p>The safety threshold of urine fluoride levels in the subgroup TT: 1.73 mg/L (1.51-1.97)</p>	$p = 0.236$ $p = 0.053$ $p = 0.236$ $p = 0.220$ $p < 0.001$ $p = 0.001$	Positive	Children/ adolescents
Kousik 2016 [86]	Correlation between exposure dose and IQ: $r = -0.343$	$p < 0.01$	Positive	Children/ adolescents
Mustafa 2018 [72]	Correlation between average level of fluoride in drinking water (mg/L) and <u>average school performance</u> 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 <u>prevalence of high school performance score</u> (%): Overall score: $r = -0.48$	$p = 0.012$		
Till 2020 [48]	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: <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Formula-fed: (b = -7.93, 95% CI: -12.84, -3.01) • Breastfed: (b = -6.30, 95% CI: -10.92, -1.68) 	Significant	Positive	Children/ adolescents
Wang 2020 [49]	Change in IQ scores per 1 mg/L increment of water fluoride <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • Water fluoride (1.00–1.90): -3.07 (-5.64, -0.49), $p = 0.02$ 	Significant	Positive	Children/ adolescents
Yu 2018 [77]	Odds (95% CI) of having excellent IQ level per 0.5 mg/L increment of fluoride in water; normal IQ is the control <ul style="list-style-type: none"> • 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
Goodman 2022 ^[6]	Cohort	Mexico	Mother-child pairs	Positive	1997-1999 2001-2003
Feng 2022 ^[4]	Cross-sectional	China	Children	Positive	2017
Ibarluzea 2022 ^[8]	Cohort	Spain	Mother-child pairs	Positive	1997–2008
Kaur 2022 ^[9]	Cross-sectional	India	Children	Positive	2011
Saeed 2022 ^[13]	Cross-sectional	Pakistan	Children and adolescents	Positive	NR
Ahmad 2021 ^[3]	Cross-sectional	Pakistan	Children	None	NR
Farmus 2021 ^[21]	Cohort	Canada	Mother-child pairs	Positive	2008-2011
Wang 2021 ^[32]	Cross-sectional	China	Children	Positive	2015
Yani 2021 ^[33]	Cross-sectional	Indonesia	Children	Positive	NR
Yu 2021 ^[34]	Cross-sectional	China	Children	Positive	2015
Zhao 2021 ^[35]	Cross-sectional	China	Children	Positive	2018
Cui 2020 ^[37]	Cross-sectional	China	Children/ adolescents	Non-significant	2014 - 2018
Till 2020 ^[48]	Cohort	Canada	Children/ adolescents	Positive	2008-2011
Wang 2020 ^[49]	Cross-sectional	China	Children/ adolescents	Positive	2015
Soto-Barreras 2019 ^[62]	Cross-sectional	Mexico	Children/ adolescents	None	2017
Cui 2018 ^[67]	Cross-sectional	China	Children/ adolescents	Positive	2014-2015
Mustafa 2018 ^[72]	Cross-sectional	Sudan	Children/ adolescents	Possible	NR
Yu 2018 ^[77]	Cross-sectional	China	Children/ adolescents	Positive	2015
Bashash 2017 ^[79]	Cohort	Mexico	Children/ adolescents	Positive	1997-1999 2001-2003
Arulkumar 2017 ^[78]	Cross-sectional	India	Adults (fluorosis patients)	Possible	NR
Kousik 2016 ^[86]	Cross-sectional	India	Children/ adolescents	Positive	NR
Heck 2016 ^[85]	Cross-sectional	United States	Adults, children/ adolescents	None	NR

Temporality

Study	Design	Outcome, time of assessment
Goodman 2022 ^[6]	Cohort	GCI/FSIQ, PIQ, and VIQ scores across ages 4, 5 and 6–12 years
Ibarluzea 2022 ^[8]	Cohort	Results in boys suggest improved scores in cognitive domains with maternal urinary concentrations.
Farmus 2021 ^[21]	Cohort	Performance IQ at the ages of 1.9 and 4.4 years
Till 2020 ^[48]	Cohort	IQ scores at the age of 3-4 years old
Bashash 2017 ^[79]	Cohort	<ul style="list-style-type: none">• GCI scores at the age of 4 years old• Full-Scale IQ scores at the age of 6–12 years old
All other studies were cross-sectional (temporality is not applicable)		

Biological gradient (exposure-response)

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
Arulkumar 2017 [78]	Serum level of AChE (U/l)	P= 0.000	Possible positive	Adults (fluorosis patients)
	<ul style="list-style-type: none"> • 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	P= 0.000		
	<ul style="list-style-type: none"> • Controls: 2.41 ± 0.34 • Mild: 2.56 ± 0.31 • Moderate: 2.64 ± 0.29 • Severe: 2.87 ± 0.4 			
Bashash 2017 [79]	Change in outcome per 0.5 mg/L increase in maternal urinary fluoride levels		Positive	Children/ adolescents
	<ul style="list-style-type: none"> ○ <i>GCI: $\beta = -3.15 (-5.42, -0.87)$</i> 	<i>p = 0.01</i>		
	<ul style="list-style-type: none"> ○ <i>IQ: $\beta = -2.50 (-4.12, -0.59)$</i> 	<i>p = 0.01</i>		
	Change in outcome per 0.5 mg/L increase in child urinary fluoride levels			
	<ul style="list-style-type: none"> ○ <i>IQ – Without adjustment of maternal urinary fluoride levels: $\beta = -0.89 (-2.63, 0.85)$</i> 	<i>Non-significant</i>		

Study	Effect estimates	Statistical Significance	Effect on lowering IQ scores	Population
	<ul style="list-style-type: none"> IQ – With adjustment of maternal urinary fluoride levels $\beta = -0.77 (-2.53, 0.99)$ 	Non-significant		
Cui 2018 [67]	<p>Change (95% CI) in IQ score per log-unit increase in urinary fluoride among all participants and by subgroups</p> <p><u>Overall (N = 323)</u> $\beta = -2.47 (-4.93, -0.01), p = 0.049$ [Bootstrapped estimate: 95%CI = -4.97, 0.03]</p> <hr/> <p><u>DRD2 SNP of CC or CT (N = 279)</u> $\beta = -1.59 (-4.24, 1.05)$ [Bootstrapped estimate: 95%CI = -4.14, 0.95]</p> <hr/> <p><u>DRD2 SNP of TT (N = 44)</u> $\beta = -12.31 (-18.69, -5.94), p < 0.001$ [Bootstrapped estimate: 95%CI = -19.66, -4.96]</p> <p>The safety threshold of urine fluoride levels in the subgroup TT: 1.73 mg/L (1.51-1.97)</p>	<p>$p = 0.236$</p> <hr/> <p>$p = 0.053$</p> <hr/> <p>$p = 0.236$</p> <hr/> <p>$p = 0.220$</p> <hr/> <p>$p < 0.001$</p> <hr/> <p>$p = 0.001$</p>	Positive	Children/ adolescents
Kousik 2016 [86]	Correlation between exposure dose and IQ: $r = -0.343$	$p < 0.01$	Positive	Children/ adolescents
Mustafa 2018 [72]	Correlation between average level of fluoride in drinking water (mg/L) and <u>average school performance</u> 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 <u>prevalence of high school performance score (%)</u> : Overall score: $r = -0.48$	$p = 0.012$		
Till 2020 [48]	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: <ul style="list-style-type: none"> • Formula-fed: 9.3-point (95% CI: -13.77, -4.76) • Breastfed: 6.2-point (95% CI: -10.45, -1.94). 	Significant	Positive	Children/ adolescents
	Association remained significant upon controlling for fetal fluoride exposure <ul style="list-style-type: none"> • Formula-fed: ($\beta = -7.93$, 95% CI: -12.84, -3.01) • Breastfed: ($\beta = -6.30$, 95% CI: -10.92, -1.68) 			
Wang 2020 [49]	Fluoride exposure was inversely related to IQ scores <ul style="list-style-type: none"> • Water fluoride: $\beta = -1.59$ (95% CI: -2.61, -0.57) 	$P=0.002$	Positive	Children/ adolescents
Yu 2018 [77]	Odds (95% CI) of having excellent IQ level per 0.5 mg/L increment of fluoride in water; normal IQ is the control <ul style="list-style-type: none"> • 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

Thyroid dysfunction

Strength of association

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
Du 2021 [20]	Tvol (cm3)		<i>Positive association</i>	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		
	• Girls: β (95% CI): - 0.03 (- 0.10, 0.04)	0.381		
	• Interaction: β (95% CI): 0.01 (- 0.08, 0.10)	0.795		

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
Cui 2020 [37]	Median (q1-q3) TSH in uIU/mL by urinary fluoride levels <ul style="list-style-type: none"> < 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 [69]	Thyroid hormone (<u>Mean</u>) levels by study group (<i>A: fluorosis endemic area, B: fluorosis non-endemic area</i>) <ul style="list-style-type: none"> Free T3 (pg/ml): A: 3.125; B: 2.698 	p = 0.26	Positive	Children/adolescents
	<ul style="list-style-type: none"> Free T4 (ng/dL): A: 1.282; B: 1.193 	p = 0.41		
	<ul style="list-style-type: none"> TSH (µIU/m): A: 3.849; B: 2.588 	p = 0.02		
	<ul style="list-style-type: none"> Percent (%) of thyroid hormone level derangement: A: 67.5; B: 54 			
Rathore 2018 [75]	<ul style="list-style-type: none"> Exposure groups: <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> <u>Gp 1: 2.66 pg/mL ±0.46, [2.11 – 3.89]</u> <u>Gp 2: 2.73 pg/mL ±0.36, [2.13 – 3.56]</u> <u>Gp 3: 2.84 pg/mL ±0.46, [2.02 – 4.26]</u> <u>Gp 4: 3.06 pg/mL ±0.78, [1.91 – 4.42]</u> Free T4: mean ±SD, [range] (ng/dL) 	P value: NR	Positive	Children/adolescents

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	<p><u>Gp 1:</u> 0.98 ng/dL ±0.21, [0.79 – 1.79]</p> <p><u>Gp 2:</u> 1.02 ng/dL ±0.26, [0.78 – 1.89]</p> <p><u>Gp 3:</u> 1.11 ng/dL ±0.28, [0.76 – 1.98]</p> <p><u>Gp 4:</u> 1.22 ng/dL ± 0.33, [0.75 – 1.89]</p> <p>• TSH: Mean ± SD, [range] (µIU/mL)</p> <p><u>Gp 1:</u> 1.33 µIU/mL ±0.78, [0.4 – 2.99]</p> <p><u>Gp 2:</u> 1.64 µIU/mL ±0.88, [0.29 – 3.76]</p> <p><u>Gp 3:</u> 1.86 µIU/mL ±0.77, [0.76 – 3.74]</p> <p><u>Gp 4:</u> 1.91 µIU/mL ±1.10, [0.75 – 4.99]</p>			
Wang 2020 [49]	<p>Every 1 mg/L increment of water fluoride was associated with</p> <ul style="list-style-type: none"> • 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
	<p>Every 1 mg/L increment of urinary fluoride was associated with</p> <ul style="list-style-type: none"> • 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)		

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
Malin 2018 [71]	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 = 0.01 (one-tailed)	Possible positive	Children/ adolescents and adults

Consistency

Study	Design	Country	Population	Time period
Du 2021 [20]	Cross-sectional	China	Children/ adolescents	2017
Cui 2020 [37]	Cross-sectional	China	Children/ adolescents	2014 - 2018
Kumar 2018 [69]	Cross-sectional	India	Children/ adolescents	NR
Rathore 2018 [75]	Cross-sectional	India	Children/ adolescents	NR
Wang 2020 [49]	Cross-sectional	China	Children/ adolescents	2015
Malin 2018 [71]	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 ^[69]	Thyroid hormone (<u>Mean</u>) levels by study group (A: fluorosis endemic area, B: fluorosis non-endemic area)	p = 0.26		
	• Free T3 (pg/ml): A: 3.125; B: 2.698			
	• Free T4 (ng/dL): A: 1.282; B: 1.193	p = 0.41		
	• TSH (μIU/m): A: 3.849; B: 2.588	p = 0.02		
	• Percent (%) of thyroid hormone level derangement: A: 67.5; B: 54			
Rathore 2018 ^[75]	<ul style="list-style-type: none"> Exposure groups: <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> <u>Gp 1: 2.66 pg/mL ±0.46, [2.11 – 3.89]</u> <u>Gp 2: 2.73 pg/mL ±0.36, [2.13 – 3.56]</u> <u>Gp 3: 2.84 pg/mL ±0.46, [2.02 – 4.26]</u> <u>Gp 4: 3.06 pg/mL ±0.78, [1.91 – 4.42]</u> Free T4: mean ±SD, [range] (ng/dL) <ul style="list-style-type: none"> <u>Gp 1: 0.98 ng/dL ±0.21, [0.79 – 1.79]</u> <u>Gp 2: 1.02 ng/dL ±0.26, [0.78 – 1.89]</u> 	P value: NR	Positive	Children/ adolescents

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	<p><u>Gp 3:</u> 1.11 ng/dL \pm0.28, [0.76 – 1.98]</p> <p><u>Gp 4:</u> 1.22 ng/dL \pm 0.33, [0.75 – 1.89]</p> <p>• TSH: Mean \pm SD, [range] (μIU/mL)</p> <p><u>Gp 1:</u> 1.33 μIU/mL \pm0.78, [0.4 – 2.99]</p> <p><u>Gp 2:</u> 1.64 μIU/mL \pm0.88), [0.29 – 3.76]</p> <p><u>Gp 3:</u> 1.86 μIU/mL \pm0.77, [0.76 – 3.74]</p> <p><u>Gp 4:</u> 1.91 μIU/mL \pm1.10, [0.75 – 4.99]</p>			
Wang 2020 [49]	<p>Every 1 mg/L increment of water fluoride was associated with</p> <ul style="list-style-type: none"> • 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
	<p>Every 1 mg/L increment of urinary fluoride was associated with</p> <ul style="list-style-type: none"> • 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 [71]	Change (95%CI) in serum TSH (μ IU/L) per unit increase in UFsg (mg/L)	p = 0.43	Possible positive	Children/ adolescents and

Study	Effect estimates	Statistical Significance	Effect on thyroid dysfunction	Population
	No iodine deficiency: $\beta = -0.02$ (-0.19, 0.15)			adults
	Iodine deficiency: $\beta = 0.36$ (-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 ³² (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) ³³	0, 10, 20	None (serum T3, T4 and TSH levels were assessed)	None

³² “[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](#))

³³ 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.

Kidney dysfunction

Strength of association

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
Nanayakkara 2020 [44]	<p>Mean serum fluoride level (\pmSD) by CKDu stage</p> <ul style="list-style-type: none"> • Stage 0: 35.5 μg/L (\pm16.3) • Stage 1: 38.1 μg/L (\pm18.1) • Stage 2: 53.9 μg/L (\pm34.2) * • Stage 3: 82.8 μg/L (\pm41.9) * • Stage 4: 123.4 μg/L (\pm59.9) * • Stage 5: 123.9 μg/L (\pm52.6) * 	* $p < 0.05$ compared to controls	Possible	Adult non-dialysis CKDu cases
Fernando 2019 [52]	<ul style="list-style-type: none"> • Serum fluoride: Mean \pmSD [range] mg/L <i>CKDu patients: 1.43 \pm1.2 [0.47 – 9.58]</i> <i>Controls: 1.07 \pm0.3 mg/L [0.51 – 1.92]</i> <i>p = 0.000 (showed a significant difference based on CKDu stage but not with sex or age)</i> • Urinary fluoride: Mean \pmSD [range] mg/L <i>CKDu patients: 1.53 \pm0.8 [0.45 – 6.92]</i> <i>Controls: 1.26 \pm0.63 [0.36 – 3.80]</i> 	$p = 0.000$	Possible	Adult non-dialysis CKDu cases
Malin 2019 [57]	<p>1 mg/L increase in water fluoride was associated with:</p> <ul style="list-style-type: none"> • 0.93 mg/dL lower blood urea nitrogen concentration (95% CI: 	$p = 0.007$	Possible	Children/adolescents

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	-1.44, -0.42).			
	<ul style="list-style-type: none"> eGFR: -1.03 mL/min/m² (95% CI: -2.93, 0.87) <i>Water fluoride was log₂ transformed in this model.</i> 	p > 0.99		
	<ul style="list-style-type: none"> SUA: 0.05 mg/dL (95% CI: -0.07, 0.18) 	p > 0.99		
	<ul style="list-style-type: none"> ACR: -0.01 mg/g (95% CI: -0.07, 0.06) <i>Water fluoride and outcome variables were log₂ transformed.</i> 	p > 0.99		
	1 μmol/L increase in plasma fluoride was associated with:			
	<ul style="list-style-type: none"> 10.36 mL/min/1.73m² lower estimated glomerular filtration rate (95% CI: -17.50, -3.22) 	p=0.05		
	<ul style="list-style-type: none"> 0.29 mg/dL higher serum uric acid concentration (95% CI: 0.09, 0.50) 	p=0.05		
	<ul style="list-style-type: none"> 1.29 mg/dL lower blood urea nitrogen concentration (95%CI: -1.87, -0.70) 	p < 0.001		
Jimenez-Cordova 2018 ^[68]	Change in outcome (p-value) per unit increase of fluoride in water (mg/L) and urine (μg/mL)		Possible	Adults
	<ul style="list-style-type: none"> ALB (μg/mL) <i>Water: β= 1.20</i> <i>Urine: β= 0.56</i> 	p= <0.001		
	<ul style="list-style-type: none"> Cys-C (mg/mL) <i>Water: β= 0.03</i> <i>Urine: β= 0.022</i> 	p= 0.005		
	<ul style="list-style-type: none"> OPN (mg/mL) 	p= 0.001		

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	<i>Water: $\beta= 0.10$</i>	$p= 0.028$		
	<i>Urine: $\beta= 0.038$</i>	$p= 0.041$		
	• CLU ($\mu\text{g/mL}$)			
	<i>Water: $\beta= 0.09$</i>	$p= 0.118$		
	<i>Urine: $\beta= 0.07$</i>	$p= 0.100$		
	• KIM-1 (ng/mL)			
	<i>Water: $b= 0.045$</i>	$p= 0.162$		
	<i>Urine: $b= 0.048$</i>	$p= 0.008$		
	• TFF-3 (ng/mL)			
	<i>Water: $\beta= 2.88$</i>	$p= 0.010$		
	<i>Urine: $\beta= 1.14$</i>	$p= 0.115$		
	• eGFR (mL/min/1.73 m^2)			
	<i>Water: $\beta= 0.19$</i>	$p= 0.675$		
	<i>Urine: $\beta= 0.49$</i>	$p= 0.030$		

Consistency

Study	Design	Country	Association	Population	Time period
Nanayakkara 2020 [44]	Cross-sectional	Sri Lanka	Possible	Adult CKDu cases	NR
Fernando 2019 [52]	Case-control	Sri Lanka	Possible	Adult non-dialysis CKDu cases	NR
Jimenez-Cordova 2019 [53]	Cross-sectional	Mexico	Inconclusive	Children/ adolescents	2015
Malin 2019 [57]	Cross-sectional	United States	Possible	Children/ adolescents	2013–2016
Jimenez-Cordova 2018 [68]	Cross-sectional	Mexico	Possible	Adults	2013
Cardenas-Gonzalez 2016 [83]	Cross-sectional	Mexico	None	Children/ adolescents	2014

Biological gradient (exposure-response)

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
Nanayakkara 2020 [44]	<p>Mean serum fluoride level (\pmSD) by CKDu stage</p> <ul style="list-style-type: none"> Stage 0: 35.5 μg/L (\pm16.3) Stage 1: 38.1 μg/L (\pm18.1) Stage 2: 53.9 μg/L (\pm34.2) * Stage 3: 82.8 μg/L (\pm41.9) * Stage 4: 123.4 μg/L (\pm59.9) * Stage 5: 123.9 μg/L (\pm52.6) * 	* $p < 0.05$ compared to controls	Possible	Adult non-dialysis CKDu cases
Fernando 2019 [52]	<ul style="list-style-type: none"> Serum fluoride: Mean \pmSD [range] mg/L <i>CKDu patients: 1.43 \pm1.2 [0.47 – 9.58]</i> <i>Controls: 1.07 \pm0.3 mg/L [0.51 – 1.92]</i> <i>p = 0.000 (showed a significant difference based on CKDu stage but not with sex or age)</i> Urinary fluoride: Mean \pmSD [range] mg/L <i>CKDu patients: 1.53 \pm0.8 [0.45 – 6.92]</i> <i>Controls: 1.26 \pm0.63 [0.36 – 3.80]</i> 	$p = 0.000$	Possible	Adult non-dialysis CKDu cases
Malin 2019 [57]	<p>1 mg/L increase in water fluoride was associated with:</p> <ul style="list-style-type: none"> 0.93 mg/dL lower blood urea nitrogen concentration (95% CI: -1.44, -0.42). eGFR: -1.03 mL/min/m² (95% CI: -2.93, 0.87) <i>Water fluoride was log₂ transformed in this model.</i> 	$p = 0.007$	Possible	Children/adolescents

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	<ul style="list-style-type: none"> SUA: 0.05 mg/dL (95% CI: -0.07, 0.18) 	p > 0.99		
	<ul style="list-style-type: none"> ACR: -0.01 mg/g (95% CI: -0.07, 0.06) <p><i>Water fluoride and outcome variables were log2 transformed.</i></p>	p > 0.99		
	1 µmol/L increase in plasma fluoride was associated with:			
	<ul style="list-style-type: none"> 10.36 mL/min/1.73m² lower estimated glomerular filtration rate (95% CI: -17.50, -3.22) 	p=0.05		
	<ul style="list-style-type: none"> 0.29 mg/dL higher serum uric acid concentration (95% CI: 0.09, 0.50) 	p=0.05		
	<ul style="list-style-type: none"> 1.29 mg/dL lower blood urea nitrogen concentration (95%CI: -1.87, -0.70) 	p < 0.001		
Jimenez-Cordova 2018 ^[68]	Change in outcome (p-value) per unit increase of fluoride in water (mg/L) and urine (µg/mL)		Possible	Adults
	<ul style="list-style-type: none"> ALB (µg/mL) <ul style="list-style-type: none"> Water: β= 1.20 Urine: β= 0.56 	p= <0.001		
	<ul style="list-style-type: none"> Cys-C (mg/mL) <ul style="list-style-type: none"> Water: β= 0.03 Urine: β= 0.022 	p= 0.005		
	<ul style="list-style-type: none"> OPN (mg/mL) <ul style="list-style-type: none"> Water: β= 0.10 Urine: β= 0.038 	p= 0.028		
		p= 0.041		

Study	Effect estimates	Statistical Significance	Effect on kidney dysfunction	Population
	• CLU ($\mu\text{g/mL}$)			
	<i>Water: $\beta= 0.09$</i>	p= 0.118		
	<i>Urine: $\beta= 0.07$</i>	p= 0.100		
	• KIM-1 (ng/mL)			
	<i>Water: $b= 0.045$</i>	p= 0.162		
	<i>Urine: $b= 0.048$</i>	p= 0.008		
	• TFF-3 (ng/mL)			
	<i>Water: $\beta= 2.88$</i>	p= 0.010		
	<i>Urine: $\beta= 1.14$</i>	p= 0.115		
	• eGFR (mL/min/1.73 m ²)			
	<i>Water: $\beta= 0.19$</i>	p= 0.675		
	<i>Urine: $\beta= 0.49$</i>	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 ³⁴ were assessed)	None
Mice (subchronic) (631)	0, 150,	None (kidney function was assessed)	None
<i>Rat (subchronic) (1215)</i>	<i>0, 15</i>	<i>Histology</i>	<i>Single dose (tier-2 study)</i>

³⁴ Blood urea nitrogen and creatinine levels

Sex hormones

Strength of association

Study	Effect estimates	Statistical Significance	Effect on male reproduction	Population
Bai 2020 [36]	<ul style="list-style-type: none"> • Compared with subjects at the first tertile of plasma fluoride, percent changes (95% CI) in testosterone were: <ul style="list-style-type: none"> ○ Second tertile: –8.08% (–17.36%, 2.25%) ○ Third tertile: –21.65% (–30.44%, –11.75%) <hr/> <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> ○ 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
Sex steroid hormones in serum		<0.001		
<ul style="list-style-type: none"> • Testosterone (ng/dL) <ul style="list-style-type: none"> ○ 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) 				

Study	Effect estimates	Statistical Significance	Effect on male reproduction	Population
	<ul style="list-style-type: none"> • Estradiol (pg/mL) <ul style="list-style-type: none"> ○ 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		
	<ul style="list-style-type: none"> • SHBG (nmol/L) <ul style="list-style-type: none"> ○ 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) ○ Female adolescents: 54.01 (50.78, 57.25) 	<0.001		
An 2019 [50]	<p>Water fluoride (Mean ± SD)</p> <ul style="list-style-type: none"> • 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
	<p>Urinary fluoride (Mean ± SD), mg/L</p> <ul style="list-style-type: none"> • HEG: 2.66 ± 1.03 • LEG: 0.95 ± 0.31 	P = <0.001		
	<p>Reproductive hormones (Mean ± SD), nmol/L</p> <p>ABP</p> <ul style="list-style-type: none"> • HEG: 19.86 ± 22.46 	P = 0.144		

Study	Effect estimates	Statistical Significance	Effect on male reproduction	Population
	<ul style="list-style-type: none"> • LEG: 24.04 ± 26.94 			
	SHBG	P = 0.012		
	<ul style="list-style-type: none"> • HEG 30.07 ± 28.32 			
	<ul style="list-style-type: none"> • LEG 35.90 ± 28.58 			

Consistency

Study	Design	Country	Population	Time period
An 2019 [50]	Cross-sectional	China	Adults (males)	2011-2012

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 (subchronic) (237)	0, 10, 50, 100	Sperm quality ³⁵ , testicular 3β-HSDH, serum testosterone levels, histology of testis and counts of germ cells	Altered at all doses tested
Rat (subchronic) (238)	0, 5, 110	Sperm quality ³⁶ , serum testosterone and histology of testis	Altered at all doses tested
Mice (subchronic) (211)	0, 11, 22, 45	Sperm quality ³⁷ , serum testosterone and histology of testis	Altered at all doses tested
Mice (subchronic) (924)	0, 11, 22, 45	Ultra-structure of testicular tissues ³⁸ and mitophagy in Leydig cells	Altered at all doses tested
Mice (subchronic) (925)	0, 11, 22, 45	Testicular morphology and ultrastructure of sperm	Altered at higher doses
Mice (subchronic) (1595)	0, 13, 32, 68	Sperm quality ³⁹ , hyperactivation and [Ca ²⁺] levels	Altered at higher doses
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 ⁴⁰	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 ⁴¹ and histology of testis	Altered at higher doses

³⁵ Total Sperm Count, Motility, and Abnormality

³⁶ Sperm motility and abnormality

³⁷ The sperm count, the abnormal ratio of sperm and sperm head

³⁸ Mitochondrial structural impairment in germ cells, Sertoli cells and Leydig cells

³⁹ Sperm motility, count and survival

⁴⁰ Sperm count, viability and morphology

⁴¹ Sperm count, motility and viability

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