The Adverse Effect of Fluoride on Children's Intelligence: A Systematic Review

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The authors conducted a systematic review on published studies to date to investigate the effect of fluoride exposure on children's intelligence quotient (IQ) scores. PSYCHINFO, Web of Science, MEDLINE, SCI, and the China National Knowledge Infrastructure (CNKI) search engines were employed for all documents published up to 2012, in English and in Chinese. In total, 38 studies of fluoride exposure and children's scores on IQ tests were included in this review. The weighted mean effect size (WMES) on children's IQ scores between higher and lower regions of fluoride exposure was -.46 (CI 95% -.57 to -.35; $p<.001$) equivalent to 6.9 IQ points. Sensitivity analyses showed that after excluding studies that had other elements contaminations, the adverse effects of fluoride exposure on children's intelligence remained to be significant. Further, six of the studies reported significant negative correlations between fluoride in the body and intelligence. The evidence suggests that fluoride in drinking water is a serious public health hazard.

Key Words: Fluoride; Intelligence; Systematic Review; Meta-analysis.

1. Introduction

Research on the adverse effect of fluoride on children's intelligence quotient (IQ) was first reported by Ren and colleagues in a Chinese journal in 1989 (Ren, Li, & Liu, 1989). Since then, a number of studies on this topic have been published, most of these studies are in Chinese. Little is known among intelligence researchers in western countries of work in China and elsewhere on the adverse effect of fluoride

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in drinking water on intelligence. There is no mention of this in the recent textbooks on intelligence by Hunt (2011), Mackintosh (2011) and Sternberg and Kaufman (2011).

The reason that the possibly adverse effect of fluoride in drinking water on intelligence has not been researched in western countries is that for the last half century fluoride has been added to reservoirs to reduce dental decay. The effect of this has been that the whole population has been exposed to fluoride and possibly adverse effects cannot be assessed. Fluoride has not been added to reservoirs in China. Exposure to fluoride in some regions of China is principally caused by drinking water where the groundwater in the unconfined aquifer, which has higher fluoride concentration, is the main source of drinking water for local residents (Wang & Huang, 1995; Zhang, Hong, Zhao, Lin, Zhang, & Dong, 2003) or by the use of fluoride contaminated coal for drying grain (Liang, Ji, & Cao, 1997). In other regions wood is used for drying grain and this does not produce fluoride, or grain is not dried. Similar situations are seen in several other developing countries. For example, Davangere district in Karnataka state, India, is considered to be naturally fluoridated area according to studies conducted by the Rajeev Gandhi National Drinking Water Mission, New Delhi (Chandrashekar & Anuradhan, 2004). This makes it possible to compare the intelligence of children in regions with greater and lesser exposure to fluoride.

Previous epidemiological studies have shown the adverse effects of fluoride on brain and central nervous system causing memory deficits and may lead to neural damage, including morphological alterations in brain cells, lipid peroxide, free radical, and DNA damage, and may affect brain function, causing disruption of certain neurotransmitters and receptors in nerve cells, and increasing numerical density of the neuron volume and the nucleus-cytoplasm ratio of the neurons (Cao, Ma & Wang, 2007; Du, Wan, Cao, & Liu, 1992;

Yang & Ye, 2006; Yu, Yang, Dong, Wan, Zhang, & Liu, 1996).

In a recent review by Barbier, Arreola-Mendoza, and Del Razo (2010) on the molecular mechanisms of fluoride toxicity, the authors showed that fluoride can induce oxidative stress and modulate intracellular redox homeostasis, lipid peroxidation and protein carbonyl content, as well as alter gene expression and cause apoptosis (Barbier, et al., 2010). Other studies have reported that fluoride exposure has caused delay in physical development (Xu & Huo, 2000) and retarded head development, based on measurement of the circumference (Wang,Yang, Jia, & Wang, 1996).

Hence, our objective in this paper is to review the extant studies on this topic through conducting a systematic review and meta-analysis, to investigate the magnitude of the adverse effect of fluoride exposure on children's intelligence.

2. Method

PSYCHINFO, Web of Science, MEDLINE, SCI, and the China National Knowledge Infrastructure (CNKI) search engines were examined for papers using the following keywords: fluoride and intelligence, fluoride and cognitive development, and fluoride and IQ. This produced 44 studies carried out between 1989 and 2012 on the extent of exposure to fluoride in drinking water and children's intelligence. A total of six studies were excluded (see reasons for exclusion in Appendix 1), and the remaining 38 studies were used for this review.

IQ measures and procedures

The IQ tests used in the studies include the Wechsler Intelligence Test, the Raven's Standard Progressive Matrices, and the Binet-Siman test. Many of the Chinese studies used the Chinese Standardized Raven Test, Rural Version, an adaptation of Ravens Progressive Matrices by Wang, Di and Qian (1989).

Regarding the testing environment and quality control, almost all studies mentioned that IQ tests were measured in accordance with the guidelines of the specific measure used, testers were well trained, and children in each study were tested individually and scored based on standards suited to their grade levels. Apart from this, two studies mentioned that IQ was tested in a double-blind, or blind manner. Among the 38 studies reviewed, 28 (%74) studies used randomly selected samples. In terms of confounding factors, 32 (%84) studies mentioned that the high fluoride and reference groups were compatible in various social, economic, and environmental conditions, with no other health problems (acute or chronic diseases not related to fluoride), and were free from other sources of high fluoride intake, such as brick tea consumption.

Statistical analysis

Comprehensive meta-analysis (version 2) was used to estimate the standardised weighted mean effect size. The fixed-effect model uses Mantel-Haenszel method, and the random-effect model uses DerSimonian-Laird methods (Petitti, 1994). We tested for heterogeneity in effect sizes, and conducted sensitivity analyses excluding studies which had other element exposures in addition to fluoride (Breierova & Choudhari, 1996). Publication bias test was performed between studies, detecting the presence of publication bias and assessing its impact on the analysis (Light, Singer, & Willett, 1994).

3. Results

The characteristics of the 38 Chinese studies and studies elsewhere included are summarized in Table 1 and Table 2 respectively. This gives the reference, the region in which the study was carried out, the age of the sample, some details exposure of the samples to fluoride, the IQs or other cognitive scores of the samples exposed to higher and lower amounts of fluoride, the differences in the IQs or other cognitive scores of the samples exposed to higher and lower amounts of fluoride expressed as *ds* (standard deviation units)

Table 1. Chinese studies on fluoride exposure and children's IQ

	Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
1.	[A]Ren, et al., 1989	Shandong Province	High fluoride & low iodine zone and Low iodine only zone	Not specified	8-14	High F & low iodine area	160	64.8±20.4 ≥90=21.9% <90=78.1%	.95	Wechsler Intelligence Test	Children in a high fluoride and low iodine area had significantly lower IQ scores than children in an area with low iodine only
						Low iodine only area	169	85.0±22.3 ≥90=48.5% <90=51.5%			
2.	Qin, et al., 1990	Hubei Province	Well water with varying levels of fluoride	High F area 2.1-4.0 mg/L	9-10.5	High F area	141	≥90=24.1% <90=75.9%	-	CRT [a]	Both high and low fluoride levels had an effect on child intelligence: fluoride levels greater than 2.0 mg/L or less than 0.2 mg/L manifested intellectual deficits as compared to the
				Very low F area 0.1-0.2 mg/L		Very low F area	147	≥90=27.2% <90=72.8%			
				Normal F area 0.5-1.0 mg/L		Normal F area	159	≥90=57.9% <90=42.1%			

	Authors	Region	Fluoride exposure: Assessment	Fluoride exposure: Range	Age range	Number		IQ: Mean±SD Rank	*d*	Outcome measures	Results
											control group
3.	Chen, et al., 1991	Linyi, [†]Shanxi Province	Drinking water/ Dental fluorosis	High F area 4.55 mg/L Dental Fluorosis rate: 85% Normal F area 0.89 mg/L Dental Fluorosis rate: 25%	7	High F area	-	90.03±11.44	.35	CRT-RC [b]	IQ scores of the children living in the high-fluoride level area were significantly lower than those children living in the normal fluoride level area
						Normal F area	-	94.15±12.06			
					8	High F area	-	92.01±11.76	.67		
						Normal F area	-	101.33±16.22			
					9	High F area	-	98.96±14.66	.04		
						Normal F area	-	99.48±11.51			
					10	High F area	-	98.90±15.90	.32		
						Normal F area	-	104.14±17.34			
					11	High F area	-	100.68±11.49	.08		
						Normal F area	-	101.65±14.16			
					12	High F area	-	100.55±12.28	.52		
						Normal F area	-	107.39±14.08			
					13	High F area	-	114.40±12.57	.36		
						Normal F area	-	109.63±14.22			
					14	High F area	-	106.38±10.33	.80		
						Normal F area	-	114.52±9.90			
					7-14	High F areas	320	100.24±14.52	.26		
						Normal F areas	320	104.03±14.95			

	Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
4.	©Guo, et al., 1991	Hunan Province	Fluoride poisoning in coal burning area Blood serum	High F coal burning area fluoride content 118.1-1361.7 mg/kg;	7-9	High F area Control area	20 19	77.30±8.52 83.95±8.53	.78	Chinese Binet	IQ scores of the children living in the coal burning area were significantly lower than those children living in the normal fluoride level area
				serum F level 0.15±0.05 mg/L	10-11	High F area Control area	20 26	76.73±12.87 81.15±10.21	.43		
				Control area used wood; serum F level 0.10±0.07 mg/L	12-13	High F area Control area	20 16	76.10±11.26 78.75±12.00	.23		
					7-13	High F areas Control area	60 61	76.7±11.04 81.4±10.43	.44		
5.	*ALin, et al., 1991	Xinjiang Uyghur Autonomous Region	Drinking Water/ Urine/ Dental fluorosis/ Goiter	Relatively high F and low I area 0.88/ 2.6±1.1 mg/L Fluorosis rate: 70.80%	7-14	Relatively high F and low iodine area Goiter rate: 54.40%	33	71.09±6.84	2.03	CRT-RC[b]	IQ scores of the children living in the relatively high fluoride and low iodine area were significantly lower than those children living in the area with iodine supplemented
						Low iodine area 1 Low iodine area 2 Goiter rate: 60.93%	47 39	79.29±12.17 77.32±11.15	1.11 1.29		
				Low I only areas 0.34/1.3-		Iodine supplement control area Goiter rate: 24.28%	39	95.76±17.52			

	Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
				1.6±0.8 mg/L Fluorosis rate: 16.00% Control area 0.34/ 1.6±1.3 mg/L							
6.	*ASun, et al., 1991	Guiyang, Guizhou Province	High F-Al combined toxicosis area Dental fluorosis	High F area Fluorosis rate: 98.36% Normal F area Fluorosis rate: not specified	≤7	High F-Al area	18	80.72±6.58	.69	Draw a Man	IQ scores of the children living in the high fluoride and high aluminium area were significantly lower than those children living in the normal F-Al area in ≤7 group; high F-Al may influence the development of the brain during the early year, and the intelligence of the children in the endemic
						Normal F area	41	85.85±10.72			
					8	High F-Al area	23	77.17±9.87	.58		
						Normal F area	48	82.96±8.32			
					9	High F-Al area	30	71.80±11.62	.71		
						Normal F area	26	79.31±9.59			
					10	High F-Al area	41	71.76±12.50	1.03		
						Normal F area	51	84.81±12.87			
					11	High F-Al area	32	69.28±8.76	1.29		
						Normal F area	36	81.92±10.79			
					12	High F-Al area	52	70.00±11.98	.64		
						Normal F area	22	77.41±11.00			
					≤7-12	High F-Al areas	196	72.35±11.47	.95		

	Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
				0.5 mg/kg							combined
9.	*AXu, et al., 1994	Shandong Province	Drinking water/ Dental fluorosis/ Goiter	High F-I area 3.9 mg/L Fluorosis	8-14	High F-I area Goiter rate: 11.2%	30	80.31±7.55	.42	Binet-Siman	IQ scores of the children living in the high fluoride
				rate: 99% High F only area 1.8		High F only area Goiter rate: 0%	97	79.25±2.25	.81		and high iodine area, the high fluoride only
				mg/L Fluorosis rate: 95%		High F & low I area Goiter rate: 30.1%	29	69.40±20.40	.98		area, and the high fluoride and low iodine area
				High F & low I area 2.0 mg/L		Low F & high I area Goiter rate: 22.4%	32	81.25±0.92	.51		were significantly lower than children of the
				Fluorosis rate: 97% Low F &		Low F only area Goiter rate: 0.8%	21	80.21±8.27	.42		control group; there was no significant IQ
				high I area 0.5 mg/L Fluorosis		Low F-I area Goiter rate: 45.0%	27	76.42±7.21	.91		difference between the high-fluoride and
				rate: 45% Low F only area		Low I only area Goiter rate: 10.6%	62	75.17±14.16	.74		high iodine group and the high fluoride
				0.38 mg/L Fluorosis rate: 31%		Control group	32	83.83±9.10			only group, but significant differences in

	Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
						Normal F areas	224	82.78±10.54			areas appeared to be retarded
7.	*An, et al., 1992	Baotou, Inner Mongolia Autonomous Region	Drinking water	High F area 5.2-7.6 mg/L Slightly high F area 2.1-3.2 mg/L Normal F area 0.6-1.0 mg/L	7-16	High F area Slightly high F area High and slightly high F areas Normal F area	65 56 121 121	75.6±13.3 76.1±13.9 75.9±13.6 84.0±12.1	.66 .61 .63	Wechsler Intelligence Test	IQ scores of the children living in the high and slightly high levels of fluoride areas were significantly lower than children of the control group
8.	©Li, et al., 1994	Sichuan Province	Fluoride poisoning in coal burning area Fluoride content in fluoride coal cooked grain/ Dental fluorosis	High F areas 4.7 mg/kg (no dental fluorosis) 5.2 mg/kg (dental fluorosis present) 31.6 mg/kg (dental fluorosis present) Normal F area	12-13	High F group 1 High F group 2 High F group 3 High F groups 1-3 Control group	33 38 36 117 49	273.2±50.2 243.2±36.2 240.0±30.8 251.4±42.1 267.2±39.5	.13 .63 .77 .39	Index of Mental Capacity	Children of the two groups with high fluoride exposure and dental fluorosis were significantly lower in mental capacity than children of the control group and children of the high fluoride group without dental fluorosis

Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
			Low F-I area 0.5 mg/L Fluorosis rate: 12% Low I only area 0.8 mg/L Fluorosis rate: 89% Normal area 0.8 mg/L Fluorosis rate: 40%							children's IQ scores were found between the high fluoride and high iodine group and the high fluoride and low iodine group
10. AYang, et al., 1994	Huimin & Dezhou, Shandong Province	Well water/ Urine/ Dental fluorosis/ Goiter	High F-I area 2.97/ 2.08±1.03 mg/L Fluorosis rate: 35.48% Normal F-I area 0.5/ 0.82±0.56 mg/L	8-14	High F-I area Goiter rate: 3.8%	30	76.67±7.75	.51	Chinese Comparative Intelligence Test	IQ scores of the children living in the high F & high iodine area were lower than those of the children in the reference group, but the results were not significant
					Normal F-I area	30	81.67±11.97			
11. ©Li, et al.,	Anshu & Zhijin,	Fluoride poisoning	Severe fluorosis	8-13	Severe fluorosis area	230	80.3±12.9	.82	CRT-RC[b]	IQ scores of the children living in

Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
1995	Guizhou Province	in coal burning area Urine/ Dental Fluorosis Index (DFI)	area 2.69 mg/L DFI 3.2 Medium fluorosis area 2.01 mg/L DFI 2.5 Slight fluorosis area 1.81 mg/L DFI 0.8 Normal F area 1.02 mg/L DFI <0.4		Medium fluorosis area	224	79.7±12.7	.88		the severe and medium fluorosis areas were significantly lower than those of the children in the non-fluorosis area
					Slight fluorosis area	227	89.7±12.7	.02		
					All fluorosis areas	681	83.24±10.04	.56		
					Normal F area	226	89.9±10.4			
12. ˝Wang, et al., 1996	Shihezi, Xinjiang Uyghur Autonomous Region	Well water	High F area >1.0-8.6 mg/L Normal F area 0.58-1.0 mg/L	4-7	High F area	147	95.64±14.34	.37	Wechsler Intelligence Test	IQ scores of the children in the high F area were significantly lower than those of the children in the reference area
					Normal F area	83	101.23±15.84			

Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
13. *Yao, et al., 1996	Chaoyang, Liaoning Province	Drinking water	High F area 11.0 mg/L	8-12	High F area	78	92.53±12.34	.64	CRT-RC[b]	IQ scores of the children living in the high or slightly high F areas were significantly lower than those of the children in the reference area
			Slightly high F area 2.0 mg/L		Slightly high F area	188	94.89±11.15	.29		
					High and slightly high F areas	226	94.20±11.56	.34		
			Normal F area 1.0 mg/L		Normal F area	270	98.46±13.21			
14. Zhao, et al., 1996	Fenyang & Xiaoyi, †Shanxi Province	Drinking water	High F area 4.12 mg/L	7-14	High F area	160	97.69±13.00	.54	CRT-RC[b]	IQ scores of the children in the high F area were significantly lower than those of the children in the reference area
			Normal F area 0.91 mg/L		Normal F area	160	105.21±14.99			
15. *Yao, et al., 1997	Chaoyang, Liaoning Province	Drinking water	High F area 2.0 mg/L	7-12	High F area	188	94.89±11.15	.44	CRT-RC[b]	IQ scores of the children in the high F area were lower than those of the children in the reference area (p<.01); significant
			High F area (improved for 8 years)		High F area (improved for 8 years)	326	97.83±11.27	.18		
			0.33 mg/L Normal F area		Normal F area	314	99.98±12.21			

Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
			0.4 mg/L							differences in IQ scores were also found between high F area and the improved high F area (p<.05)
16. ᴀZhang,	Kuitun,	High F-As	High	4	High F-As area by age	9	94.44±7.63	.07	Draw a Man	There were
et al.,	Xinjiang	combined	F-As area	5	group	10	82.80±10.52	.41		significant
1998	Uyghur	toxicosis	(improved	6		9	82.18±6.98	.01		differences in IQ
	Autonomous	area	for 10 years)	7		6	80.89±7.57	.84		scores of the
	Region	Drinking	0.80 mg/L	8		9	80.11±7.72	.96		children between
		water	High F only	9		6	75.83±10.34	.85		high F high As
			area	10		12	70.92±8.58	2.03		group and the
			(improved							controls in age 9;
			for 10 years)	4	High F only area by	5	112.20±13.54	1.93		and between
			0.81 mg/L	5	age group	6	90.67±8.64	.35		high F high As or
			Normal F-As	6		13	83.62±7.29	.18		high F only
			area 0.58	7		8	86.62±4.66	.07		groups and the
			mg/L	8		7	88.14±12.33	.08		controls in age 10
				9		7	82.00±13.01	.20		in the three areas
				10		4	70.66±7.50	2.14		
				4	Normal F-As area by	5	94.00±5.33			
				5	age group	10	87.20±10.98			
				6		7	82.28±7.20			

Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
				7		6	87.00±6.90			
				8		5	87.33±7.31			
				9		11	84.18±9.23			
				10		8	94.88±15.08			
				4-10	High F-As area	61	80.91±10.83	.62		
					High F only area	51	85.62±13.23	.64		
					Normal F-As area	52	87.66±11.04			
17. Lu, et al., 2000	Tianjin Municipality	Drinking water/ Urine	High F area 3.15±0.61/ 4.99±2.57 mg/L Normal F area 0.37±0.04/ 1.43±0.64 mg/L	10-12	High F area	60	92.27±20.45	.63	CRT-RC[b]	IQ scores of the children living in the high fluoride area were significantly lower than those of the control group
					Normal F area	58	103.05±13.86			
18. AHong, et al., 2001	Wukang & Boxing & Zouping, Shandong Province	Drinking water/ Goiter	High F & low iodine area 2.94mg/L Low F & low iodine area 0.48 mg/L High F & high iodine	8-14	High F & low I area Goiter rate: 42.86%	28	68.38±19.12	1.03	CRT-RC[b]	The high fluoride/low iodine and the low fluoride/low iodine areas were each significantly different compared with the control
					Low F-I area Goiter rate: 32.14%	28	75.53±6.92	.91		
					High F-I area Goiter rate: 12.50%	32	79.39±6.92	.43		

Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
			area 2.85 mg/L High F only area 2.90 mg/L Normal F & iodine area 0.75 mg/L		High F only area Goiter rate: 1.18% Normal F-I area Goiter rate: 3.13%	85 32	80.58±2.28 82.79±8.98	.39		($p<0.01$) and were also significantly different compared to each other ($p<.01$)
19. *Hou, et al., 2002	Tongxu, Henan Province	Drinking water	High F area >2.1 mg/L Normal F area <0.8 mg/L	8-12	High F area Normal F area	1346 1566	≥90=50.4% <90=49.6% ≥90=58.8% <90=41.2%	-	CRT-RC[b]	High fluoride exposure had statistically significant adverse effects on children's intelligence by rank ($\chi^2=21.52$, $p<0.05$)
20. Li, et al., 2003	Baotou, Inner Mongolia Autonomous Region	Drinking water	Endemic versus control regions defined by	6-13	High F area Normal F area	720 236	92.07±17.12 93.78±14.30	.11	CRT-RC[b]	IQ scores of the children living in the endemic regions were lower than those

Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
			the Chinese Geological Office							of the children living in the control regions, but there were no significant differences
21. Xiang, et al., 2003	Sihong, Jiangsu Province	Drinking water/ Urine	High F area 2.47±0.79	8	High F area by age group	11	94.09±16.50	.65	CRT-RC[b]	IQ scores of the children in the high fluoride group were significantly lower than those in the reference group
			Range: 0.57-4.5 mg/L	9		20	91.25±14.81	.89		
				10		20	96.35±14.04	.74		
				11		43	92.77±12.43	.35		
			Normal F area 0.36±0.15	12		60	91.15±12.74	.61		
				13		68	90.94±12.27	.50		
			Range: 0.18-0.76 mg/L	8	Normal F area by age group	39	103.39±11.58			
				9		46	104.04±13.80			
				10		31	105.45±10.57			
				11		60	97.45±14.60			
				12		61	99.41±14.20			
				13		53	96.64±10.47			
			High F area by F level	8-13						
			0.75±0.1			9	99.56±14.13	.06		
			1.53±0.27			42	95.21±12.22	.41		

Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
			2.46±0.30			111	92.19±12.98	.63		
			3.28±0.25			52	89.88±11.98	.84		
			4.16±0.22			8	78.38±12.68	1.70		
					High F area (total)	222	92.02±13.00 (54-126)	.64		
					Normal F area (total)	290	100.41±13.21 (60-128)			
					Total sample	512	-	-		
22. *AWang, et al., 2005	Datong, †Shanxi Pronince	Drinking water/ Urine	High F-As areas 8.31±1.85/ 5.09 mg/L	8-12	High F-As area	91	108.09±15.99	.28	CRT-RC[b]	IQ scores of the children in the high fluoride group were significantly lower than those in the reference area
					High F only area	253	107.83±15.54	.30		
			Normal F-As area 0.48±0.23/ 1.51 mg/L		High As only area	180	102.57±16.44	.63		
					Normal F area	196	112.36±14.87			
23. *Wang, et al., 2006	Yuncheng, †Shanxi Province	Drinking water/ Urine	High F area 5.54±3.88/ 5.50±2.40 mg/L	8-12	High F area	202	107.46±15.38	.27	CRT-RC[b]	The IQ scores of the children in the high fluoride area were significantly lower than those in the reference area
			Normal F area 0.73±0.28/ 1.51±1.66 mg/L		Normal F area	166	111.55±15.19			

	Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
24.	*Fan, et al., 2007	Pucheng, Shaanxi Province	Urine	High F area 1.14-6.09 mg/L Normal F area 1.33-2.35 mg/L	7-14	High F area	42	96.11±12.00	.17		IQ scores of the children in the high fluoride area were lower than those of children in the reference area
						Normal F area	37	98.41±14.75			
25.	*ᴀWang, et al., 2007	Shanyin, †Shanxi Province	Drinking water/ Urine	High F area 3.8-11.5/ 0.2-1.1 mg/L Normal F area 1.6-11/ 0.4-3.9 mg/L	8-12	High As only area	180	95.1±16.6	.62	CRT-C2[d]	IQ scores of the children in the high fluoride area were lower than those of children in the reference area
						Medium As area	91	100.6±15.6	.28		
						High F only area	253	100.5±15.8	.28		
						Normal F area	196	104.8±14.7			
26.	*©Li, et al., 2009	Xinhua, Hunan Province	Fluoride poisoning in coal burning area Urine	Severe fluorosis area 2.34±1.13 mg/L Medium fluorosis area	8-12	Severe fluorosis area	20	93.85±18.11	.50	CRT-RC[b]	IQ scores of the children in the severe, medium, and slight fluorosis areas were significantly lower than those of children in the
						Medium fluorosis area	20	93.90±17.60	.50		
						Slight fluorosis area	20	97.30±18.56	.30		

Authors	Region	Fluoride exposure		Age range	Number		IQ	d	Outcome measures	Results
		Assessment	Range				Mean±SD Rank			
			1.67±0.66 mg/L Slight fluorosis area 1.24±0.43 mg/L Normal F area 0.96±0.52 mg/L		Slight to severe fluorosis areas	60	95.02±18.17	.43		reference area
					Normal F area	20	102.70±17.61			
27. *‡Li, et al., 2010	Henan Province	Drinking water/ Dental fluorosis	High F areas 2.47±0.75 mg/L	7-10	High F area (dental fluorosis present)	347	98.73±21.07	.07	CRT-RC[b]	In the high fluoride area, there was no significant difference in IQ scores between children with dental fluorosis and children without dental fluorosis
					High F area (no dental fluorosis)	329	97.36±18.24			
					Total number in the high F areas	676	-	-		
28. Ding, et al., 2011	Hulunbuir, Inner	Drinking water/	High F area 0.24-2.84	7-14	Total	331	-	-	CRT-RC[b]	Urine fluoride was inversely

	Authors	Region	Fluoride exposure		Age range	Number		IQ	*d*	Outcome measures	Results
			Assessment	Range				Mean±SD Rank			
		Mongolia Autonomous Region	Urine	mg/L Normal F area 0.1-3.55 mg/L							associated with IQ in the multiple linear regression model when children's age as a covariate variable was taken into account (*p*< 0.0001)
29.	‡Xiang, et al., 2011	Sihong, Jiangsu Province	Blood sample	High F area serum F level 0.08±0.02 mg/L Normal F area serum F level 0.04±0.01 mg/L	8-13	Serum F level quartile 4	127	92.1±13.4	.60	CRT-RC[b]	OR (95 CI) for IQ<80 in quartiles 1& 2 group was 2.22 (1.4-3.5), *p*<.01; OR (95 CI) for IQ<80 in quartile 4 group was 2.5 (1.9-3.3); *p*<.001
						Serum F level quartile 3	126	95.9±13.7	.31		
						Serum F level quartile 3 & 4	253	94.01±13.7	.45		
						Serum F level quartiles 1& 2	259	100.1±13.4			
30.	*Wang & Zhu, 2012	Qian'an, Jilin Province	High fluoride villages	High F area Dental fluorosis	7-12	High F area (dental fluorosis present)	458	88.52±13.29 ≥90=46.9% <90=53.1%	.71	CRT-C2	IQ scores of the children in the high F areas were

Authors	Region	Fluoride exposure: Assessment	Fluoride exposure: Range	Age range	Number		IQ: Mean±SD Rank	*d*	Outcome measures	Results
		Dental fluorosis	rate: 57.25%		High F area (no dental fluorosis)	342	95.99±16.57 ≥90=67.7% <90=32.7%	.15		significantly lower than those of the children in the reference area; In the high F areas, there were significant differences in IQ scores between children with dental fluorosis and children without dental fluorosis
			Normal F area Dental fluorosis rate: 13.19%		High F areas (total)	800	92.21±18.45 ≥90=55.6% <90=44.4%	.37		
					Normal F area	455	98.36±14.56 ≥90=62.0% <90=38.0%			

Note: F = fluoride. Al = aluminium. As = arsenic. Cre = creatinine. I = iodine. [a]CRT = Chinese Standardized Raven Test (PDBNU, 1986). [b]CRT-RC = Chinese Standardized Raven Test, rural version (Wang et al. 1989). *Papers in Chinese. Study areas had other elements condemnations (iodine, aluminium, arsenic) in addition to fluoride exposure. © Fluoride poisoning in coal burning area. ‡All study areas had high level of fluoride in drinking water. †The mean IQ of children in Shanxi province was 108.0±14.0 in 2005. [d]CRT-C2 = the Raven's Standard Progressive Matrices and Colour Progressive Matrices (Raven et al. 1983) for fluid intelligence and was widely adopted in China after modifications were made for cultural, ethnic, and language differences (Chen 2002). The same sample design as in Xiang, et al. 2003. Only children whose mothers lived in the survey location while pregnant were included.

Table 2. Studies Elsewhere on fluoride exposure and children's IQ

	Authors	Country	Fluoride exposure		Age Range	Number		IQ	*d*	Outcome measures	Results
			Assessment	Range				Mean±SD			
1.	Calderon, et al., 2000	San Luis Potosi, Mexico	Drinking water/ Urine	High F area 1.2-3.0/ mg/L	6-8	Total	61	-	-	WISC-RM[e] RO-CFT[f] CPT[g]	Urinary fluoride correlated positively with reaction time and inversely with the scores in visuospatial organization. IQ scores were not influenced by F exposure
2.	Seraj, et al., 2004	Iran	Drinking water	High F area 2.5 mg/L	7-11	High F area	41	87.9±11.0	.90	Raven's Standard Progressive Matrices	IQ scores of the children in the high fluoride group were significantly lower than those in the control group
				Normal F area 0.4 mg/L		Normal F area	85	98.9±12.9			
3.	ѧRocha-Amador, et al., 2007	Mexico	Drinking water	High F area 9.4±0.09 mg/L	6-10	High F area area	60	-	-	WISC-RM	After controlling for confounders, an inverse association was observed between
				Medium high F area 5.3±0.09 mg/L		Medium high F area	20	-	-		

				Relatively low F area 0.8±1.4 mg/L		Relatively low F area Total	52 132	- -	 -		F in urine and Performance and Verbal scores (β values = -13, -15.6 respectively)
4.	Trivedi, et al., 2007	India	Drinking water/ Urine	High F area 5.55±0.41/ 6.13±0.67 mg/L Normal F area 2.01±0.09/ 2.30±0.28 mg/L	6-9	High F area Normal F area	89 101	91.72±1.13 104.44±1.23	10.78	Raven's Standard Progressive Matrices	IQ scores of the children in the high F group were significantly lower than those in the control group
5.	Poureslam i et al., 2011	Iran	Drinking water	High F area 2.38 mg/L Normal F area 0.41 mg/L	6-9	High F area Normal F area	59 60	91.37±15.63 97.80±15.95	.41	Raven's Standard Progressive Matrices	IQ scores of the children in the high fluoride group were significantly lower than those in the control group
6.	Eswar, et al., 2011	India	High fluoride villages	High F area 2.45 mg/L Normal F area 0.29 mg/L	12-14	High F area Normal F area	68 65	86.3±12.8 88.8±15.3	.17	Raven's Standard Progressive Matrices	No significant difference in IQ scores of the children in the high F and the normal fluoride areas

7.	ѧShivaprakash, et al., 2011	India	Drinking water/ Dental fluorosis	High F area 2.5-5.5 mg/L (dental fluorosis present) Normal F area <0.5 mg/L (no dental fluorosis)	7-11	High F area	80	66.63±18.09	.50	Raven's Coloured Progressive Matrices	IQ scores of the children with dental fluorosis was significantly lower than the scores of the children without dental fluorosis
						Normal F area	80	76.36±20.84			
8.	ѧSaxena, et al., 2012	India	Drinking water/ Urine	High F areas > 4.5 mg/L 3.1-4.5 mg/L 1.5-3.0 mg/L Normal F area <1.5mg/L	12	High F areas Group 1	38	-	-	Raven's Coloured Progressive Matrices	A statistically significant difference was observed between IQ grades and water and between IQ grades and the urinary fluoride levels. Reduction in intelligence was observed with an increased water fluoride level and urinary fluoride level (P <0.001)
						Group 2	43	-	-		
						Group 3	39	-	-		
						Normal F area Group 4	50	-			

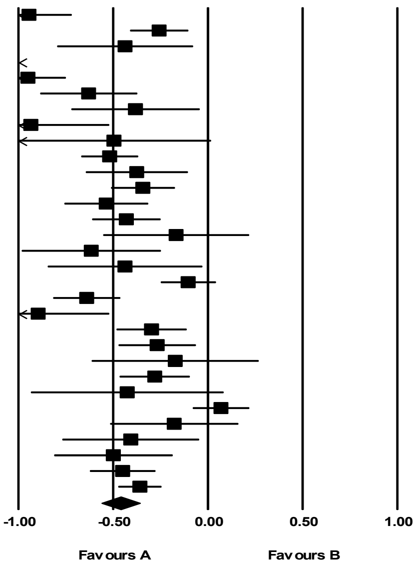
Note: [e]Wechsler Intelligence Scale for Children Revisited version for Mexico. [f]Rey Osterreith-Complex Figure Test. [g]Continuos Performance Test. ѧStudy areas had other elements condemnations (iodine, aluminium, arsenic) in addition to fluoride exposure.

Meta Analysis

Study name	Std diff in means	Lower limit	Upper limit	p-Value	Relative weight
Ren, et al., 1989	-0.944	-1.172	-0.716	0.000	3.56
Chen, et al., 1991	-0.257	-0.413	-0.101	0.001	3.95
Guo, et al., 1991	-0.437	-0.797	-0.076	0.018	2.79
Lin, et al., 1991	-1.799	-2.348	-1.250	0.000	1.89
Sun, et al., 1991	-0.950	-1.152	-0.747	0.000	3.71
An, et al., 1992	-0.629	-0.887	-0.371	0.000	3.38
Li, et al., 1994	-0.382	-0.723	-0.042	0.028	2.90
Xu, et al., 1994	-0.934	-1.350	-0.519	0.000	2.49
Yang, et al., 1994	-0.496	-1.010	0.018	0.059	2.03
Li, et al., 1995	-0.518	-0.671	-0.366	0.000	3.97
Wang, et al., 1996	-0.375	-0.647	-0.104	0.007	3.31
Yao, et al., 1996	-0.343	-0.514	-0.172	0.000	3.88
Zhao, et al., 1996	-0.536	-0.759	-0.313	0.000	3.59
Yao, et al., 1997	-0.430	-0.613	-0.248	0.000	3.81
Zhang, et al., 1998	-0.168	-0.555	0.219	0.396	2.64
Lu, et al., 2000	-0.615	-0.984	-0.246	0.001	2.74
Hong, et al., 2001	-0.437	-0.848	-0.027	0.037	2.52
Li, et al., 2003	-0.104	-0.251	0.043	0.167	3.99
Xiang, et al., 2003	-0.640	-0.819	-0.460	0.000	3.83
Seraj, et al., 2004	-0.896	-1.273	-0.518	0.000	2.70
Wang, et al., 2005	-0.297	-0.485	-0.110	0.002	3.79
Wang, et al., 2006	-0.267	-0.474	-0.061	0.011	3.68
Fan, et al., 2007	-0.172	-0.615	0.271	0.446	2.36
Wang, et al., 2007	-0.280	-0.468	-0.093	0.003	3.79
Li, et al., 2009	-0.426	-0.936	0.085	0.102	2.05
Li, et al., 2010	0.069	-0.081	0.220	0.367	3.97
Eswar, et al., 2011	-0.178	-0.518	0.163	0.307	2.90
Poureslami, et al., 2011	-0.407	-0.770	-0.044	0.028	2.77
Shivaprakash, et al., 2011	-0.499	-0.813	-0.184	0.002	3.05
Xiang, et al., 2011	-0.450	-0.625	-0.275	0.000	3.85
Wang, et al., 2012	-0.359	-0.475	-0.243	0.000	4.12
	-0.463	-0.563	-0.363	0.000	

Statistics for each study

Std diff in means and 95% CI



Meta Analysis

Figure 1. Random-effect of standardised weighted mean effect size and confidence intervals of children's IQ scores associated with fluoride exposure

where these can be calculated (in five studies this is not possible because standard deviations are not given), the IQ tests used in the study, and a summary of the results.

All the studies except one reported that children who lived in regions with greater fluoride exposure had significantly lower IQs than those who lived in regions with less fluoride exposure. The range of *d*s was from .07 to 10.8. The study with positive association indicated that the IQ scores of children who had dental fluorosis were slightly higher than children who had no dental fluorosis (d =.07), but the difference was not significant (Li, Hou, Yu, Yuan, Liu, Zhang, et al., 2010). It should be noted that in another study (Trivedi, Verma, Chinoy, Patel, & Sathawara, 2007), the SDs are unusually small (1.23 for normal and 1.13 for high fluoride areas), thus the effect size is unusually large (d=10.8). When this study was excluded, the range of *d*s was from 0.07 to 2.03.

Among the studies reviewed, two studies reported that there was a trend for higher exposure levels to have stronger IQ-reducing effects (Xiang, et al., 2011; Saxena, et al., 2012). Table 1 also shows that there appears to be some interaction effects of high fluoride and low iodine on children's IQ scores (Hong, et al., 2001; Lin, et al., 1991; Xu, et al., 1994).

We used inverse variance weighting and estimated the weighted mean effect size (WMES). The Mantel-Haenszel fixed effect model estimated that the WMES *(d)* on the 32 studies on which this can be calculated between the IQs of children in greater and lesser fluoride exposed regions was -0.41 (CI 95% -0.37 to -0.45; I^2 93.78%; p<.001) equivalent to 6.2 IQ points; and the DerSimonian-Laird random effect model showed that the WMES was -0.62 (CI 95% -.78 to -.45; p<.001) equivalent to 9.3 IQ points. When the Trivedi, et al. (2007) study was excluded from the meta-analysis, the fixed effect model estimated that the WMES was -0.40 (CI 95% -.44 to -.36; I^2 82.3%; p<.001) equivalent to 6.0 IQ points; and therandom effect model estimated that the WMES was -.46 (CI 95% -.57 to -.35; *p*<.001) equivalent to 6.9 IQ points. Detailed results for these 31 studies are shown in Figure 1. Because of the unusually small SDs resulted with an unusually large effect size of the Trivedi, et al. (2007) study, this study was excluded in the following analyses.

Sensitivity analyses

Because of the lack of homogeneity of variances among the studies, we used the random effect model for sensitivity analysis on the 31 studies in China and elsewhere. Results are shown in Table 3. First, we excluded the four studies from fluoride poisoning coal-burning areas; second, we further excluded seven studies that had other pollutions (iodine, aluminium, arsenic) apart from fluoride exposure. The results of these analyses showed a 5-7 point difference in IQ scores between the children with fluoride exposure and those in control groups. These results were similar to the ones obtained before the exclusions, indicating the consistency of these findings.

In addition to these studies comparing groups exposed to different amounts of fluoride, six of the studies also reported correlations between fluoride concentrations in the body and intelligence among individuals. The results of these are summarized in Table 4. All of the correlations were statistically significant and negative, showing that individuals with higher fluoride concentrations had lower IQs.

Further, two studies (Rocha-Amador et al., 2007; Ding, et al., 2011) also reported the inverse association between fluoride in body and children's intelligence using multiple linear regression models. In the study of Rocha-Amador and colleagues (2007), the association between amounts of fluoride in urine and individuals' IQ scores was β = -16.9; and in Ding, et al. (2011) study, it was estimated that "Each increase in 1 mg/L of urine fluoride associated with 0.59-point decrease in IQ (*p*=0.0226)" (p1942).

Table 3. Sensitivity analyses of pooled standardised weighted mean effect size (WMES) using the DerSimonian-Laird methods

Random-effect Model	Excluded Studies	n	WMES (95% CI)	IQ Point	*P*-value
Exclude coal-burning area studies	Guo et al., 1991; Li et al., 1994; Li et al., 1995; Li et al., 2009	27	-0.47 (-0.58, -0.36)	7.05	<.001
Exclude coal-burning area studies, and studies with other contaminations (iodine, aluminium, arsenic)	Guo et al., 1991; Li et al., 1994; Li et al., 1995; Li et al., 2009; Ren et al., 1989; Lin et al., 1991; Sun et al., 1991; Xu et al., 1994; Yang et al., 1994; Zhang et al., 1998; Hong et al., 2001	20	-0.37 (-0.46, -0.27)	5.55	<.001

Table 4. Correlations between fluoride concentrations and IQs among individuals

Reference	N	Assessment	r
Guo et al., 1991	242	Blood	-.205*
Lu et al., 2000	118	Urine	-.320***
Xiang et al., 2003	512	Urine	-.174**
Wang et al., 2006	368	Urine	-.119*
Li et al., 2009	140	Urine	-.476**
Saxena, et al., 2012	170	Water Urine	-.534*** -.542***

*, ** and *** denote statistical significance at $p<.05$, $p<.01$, and $p<.001$, respectively.

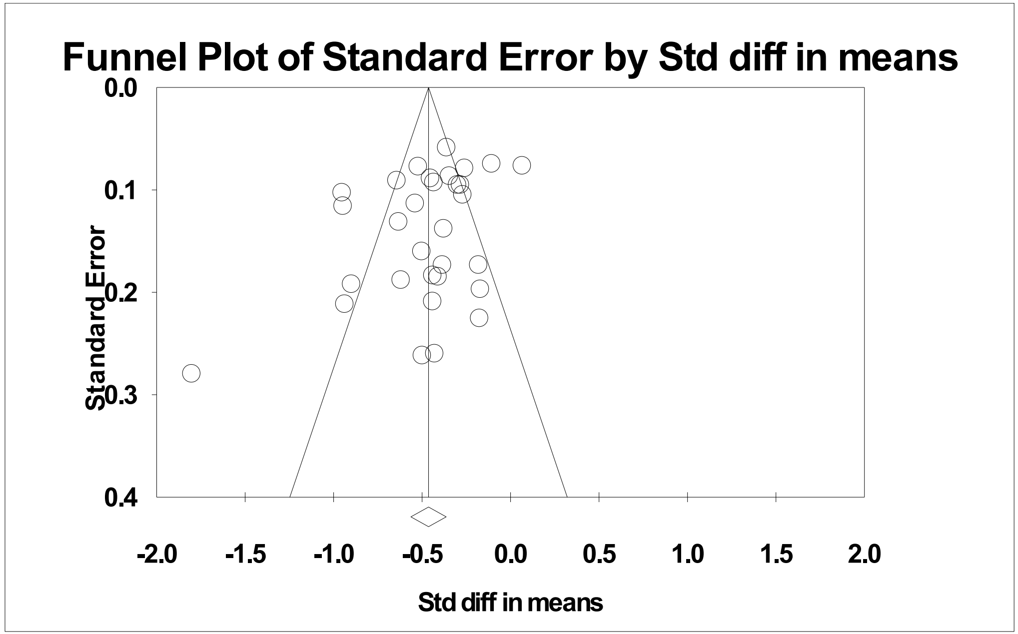


Figure 2. Funnel plot of the present study

Publication bias

Figure 2 is the funnel plot of the study. This is a plot of a measure of study size (usually standard error or precision) on the vertical axis as a function of effect size on the horizontal axis. The graph shows that the studies have distributed fairly symmetrically, except one, which shows some bias, reflecting the fact that smaller studies are more likely to be published if they have larger than average effects, which makes them more likely to meet the criterion for statistical significance.

4. Discussion

The consistency of relationship between the lower IQs of children in greater than in lesser fluoride exposed regions in all thirty-seven studies summarized in Tables 1 and 2, and the negative correlations between fluoride concentrations and IQs among individuals summarized in Table 3, establish a strong case that fluoride in drinking water impairs intelligence. The best estimate of the magnitude of this impairment is 6.9 IQ points. This is a substantial impairment and suggests that fluoride in drinking water might be a serious public health hazard in western nations where it is added to reservoirs.

The findings of the present review are in line with previous human and animal studies, which reported that fluoride exerts its adverse effects by impairing thyroid gland function and the development of the brain and central nervous system. It has been reported that fluoride impairs thyroid gland function in humans by Bürgi, Siebenhüner and Miloni (1984) and in pregnant women this can lead to children with lower IQ scores (Klein, Sargent, Larsen et al., 2001). Animal studies have reported that fluoride has adverse effects on the development of the central nervous system of the rat (Basha & Madhusudhan, 2010; Bera, Sabatini, Auteri, Flace et al., 2007; Chen & Chen, 2002). An adverse effect of fluoride on thyroid function of the rat has been reported by Basha, Rai and Begum (2011). A damaging effect of fluoride on the developmnet of the brain in mice has been reported by Bouaziz, Amara, Essefi, Croute and Zeghal (2010). Iodine is essential for the synthesis of the thyroid hormones triiodothyronine and thyroxine, which affect a number of physiological processes, including growth and development, and metabolism. Iodine-deficiency can cause decreased production of thyroid hormones, which adversely affects not only brain development, but also its functions such as attention, learning and memory (Wang, Ge, Ning, & Niu, 2009).

Other animal studies have shown that the rate and degree of DNA damage to brain cells in rats exposed to high fluoride, low iodine and their combined interaction were markedly higher (Wang, Ge, Ning, & Niu, 2009). These findings may partly explain the significant lower IQ scores of the children in the low iodine and high fluoride areas compared with the children in areas with high fluoride but sufficient iodine (Hong, et al., 2001; Xu, et al., 1994).

Although the mechanism underlying the adverse effect of fluoride on children's intelligence is unclear, this review shows that fluoride in drinking water has significant adverse effect on children's intelligence and cognitive development. This effect remains to be significant after eliminating the effects of other harmful trace elements (iodine, aluminium, and arsenic), and publication bias analysis shows that the studies reviewed are relatively free from publication bias. Future studies, especially at individual level, are required to further ascertain the associations between fluoride exposure and children's intelligence.

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Appendix 1. Excluded studies and references

Authors	Region Country	Age range	Fluoride exposure		Number		IQ	Outcome measures	Reasons for exclusion
			Assessment	Range					
1. Xu & Ho, 1991	Ningxia Hui Autonomous Region China	7-17	Drinking water	High F area 3.99 mg/L Normal F area 0.73 mg/L	High F area Normal F area	395 608	74.43 74.39	Chinese Binet	Missing SDs
2. Xu,et al., 1993	Ningxia Hui Autonomous Region	7-17	Drinking water	High F area 3.99 mg/L Normal F area 0.73 mg/L	High F area Normal F area	395 608	74.43 74.39	Chinese Binet	Duplicate the study of Xu & Ho, 1991
3. Liu, S., et al., 2000	Tianjin Municipality China	10-12	Drinking water	High F area 3.15±0.61/ mg/L Normal F area 0.37±0.04 mg/L	High F area Normal F area	60 58	92.27±20.45 103.05±13.86	CRT-RC[b]	Duplicate the study of Lu, et al., 2000
4. Wang, et al., 2001	Shandong Province China	8-14	Well water/ Urine	High F area 2.97/2.08±1.03 mg/L Normal F area	High F & high iodine area	30	76.67±7.75	Chinese Comparative Intelligence Test	Duplicate the study of Yang et al., 1994

				0.5/0.82±0.56 mg/L	Normal F & iodine area	30	81.67±11.97		
5.	Wang, et al. , 2005	Guizhou Province China	7-12	Urine	High F area 1.35±0.46 mg/L	High F zone	144	-	Raven Standard Theoretical Intelligence	Contradicting statements (F level was higher in the control zone)
					Normal F area 1.61±0.47 mg/L	Normal F zone	35			
6.	Poureslami, et al., 2011	Iran	6-9	Drinking water	High F area 2.38 mg/L	High F area	59	91.37±15.63	Raven's Standard Progressive Matrices	Duplicate the study of Poureslami, et al., 2011
					Normal F area 0.41 mg/L	Normal F area	60	97.80±15.95		

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