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A benchmark concentration analysis for manganese in drinking water and IQ deficits in children

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ABSTRACT

Background: Manganese is an essential nutrient, but in excess, can be a potent neurotoxicant. We previously reported findings from two cross-sectional studies on children, showing that higher concentrations of manganese in drinking water were associated with deficits in IQ scores. Despite the common occurrence of this neurotoxic metal, its concentration in drinking water is rarely regulated.
Objective: We aimed to apply a benchmark concentration analysis to estimate water manganese levels associated with pre-defined levels of cognitive impairment in children, i.e. drop of 1%, 2% and 5% in Performance IQ scores.
Methods: Data from two studies conducted in Canada were pooled resulting in a sample of 630 children (ages 5.9–13.7 years) with data on tap water manganese concentration and cognition, as well as confounders. We used the Bayesian Benchmark Dose Analysis System to compute weight-averaged median estimates for the benchmark concentration (BMC) of manganese in water and the lower bound of the credible interval (BMCL), based on seven different exposure-response models.
Results: The BMC for manganese in drinking water associated with a decrease of 1% Performance IQ score was 133 μg/L (BMCL, 78 μg/L); for a decrease of 2%, this concentration was 266 μg/L (BMCL, 156 μg/L) and for a decrease of 5% it was 676 μg/L (BMCL, 406 μg/L). In sex-stratified analyses, the manganese concentrations associated with a decrease of 1%, 2% and 5% Performance IQ in boys were 185, 375 and 935 μg/L (BMCLs, 75, 153 and 386 μg/L) and 78, 95, 192 μg/L (BMCLs, 9, 21 and 74 μg/L) for girls.
Conclusion: Studies suggest that a maximum acceptable concentration for manganese in drinking water should be set to protect children, the most vulnerable population, from manganese neurotoxicity. The present risk analysis can guide decision-makers responsible for developing these standards.

1. Introduction

Manganese (Mn) is an abundant, metallic element commonly present in air, soil, food, and water. It is an essential nutrient, but in excess can also interfere with the normal function of the nervous system (Avila et al., 2013). In occupational settings, manganese exposure has long been recognized as a potent neurotoxicant able to induce motor and cognitive impairments as well as neuropsychiatric symptoms (Rodier, 1955). More recently, several studies have examined the health risks arising from environmental exposures to this metal, suggesting psychological and neurological abnormalities with exposure (O'Neal and Zheng, 2015). Children are thought to be at particular risk because of

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the unique processes underway in the developing nervous system, a higher dose of exposure per body weight, and their underdeveloped homeostatic mechanisms (Zoni and Lucchini, 2013).

Several regions in North America and elsewhere around the world have high concentrations of manganese in water (Frisbie et al., 2012). Naturally elevated manganese levels can be found in groundwater due to the weathering and leaching of manganese-bearing minerals. A recent study from the U.S. Geological Survey on over 40,000 wells across the United States revealed that elevated concentrations of manganese in groundwater used for human consumption are associated with shallow, anoxic water tables and soils enriched in organic carbon (McMahon et al., 2019). It further suggested that anthropogenic nitrogen, such as fertilizers used in agriculture, may also help mobilize manganese from soil and increase its concentrations in groundwater. High manganese levels can also be observed occasionally in surface water when it is released from anoxic sediments, usually at the end of the summer in conditions of higher water temperature (Davison, 1993). Surface and ground water with elevated manganese levels have been reported due to contamination from various human activities, such leaching from composting facilities or landfills, sewage water (He et al., 1994), mining waste (Howe et al., 2004) and buried dry-cell batteries (Kawamura et al., 1941). Finally, it should be noted that a gasoline additive containing manganese was formerly used in Canada but its use has been discontinued > 15 years ago.

Mounting evidence indicates that manganese exposure from drinking water may pose risks for children's health, especially neurodevelopment (Bjorklund et al., 2017). In Bangladesh, where elevated concentrations of manganese are present in well-water, several epidemiological studies have reported associations with neurodevelopmental deficits, including more externalizing and internalizing problem behaviors (Khan et al., 2011; Rahman et al., 2017), lower academic achievement scores (Khan et al., 2012), and lower IQ scores (Wasserman et al., 2006, 2011). The currently published data do not allow determining precisely the water manganese concentration that should be considered of concern for health. Indeed, several studies reported monotonic exposure-response relations without evidence of a threshold for effect (e.g., Wasserman et al., 2006 for IQ scores; Khan et al., 2011 for externalizing problems) whereas other studies only reported group analysis showing significantly lower cognition at water manganese levels above 400 μg/L (e.g., Khan et al., 2012) and 300 μg/L (He et al., 1994).

In Canada, at levels much lower than in Bangladesh, we reported cross-sectional studies among school-age children investigating the relation between water manganese concentrations and cognition (Bouchard et al., 2011, 2018), as well as attention, hyperactive behaviors, and motor function (Oulhote et al., 2014a). Our first study was conducted in the province of Quebec ($n = 375$), where we found that higher manganese levels in both water and hair were associated with significantly lower IQ scores, with stronger manganese-related deficits for Performance IQ than Verbal IQ and stronger associations in girls than in boys (Bouchard et al., 2011). We then conducted another study in the province of New Brunswick in order to replicate the first study (Bouchard et al., 2018), but water manganese concentrations were found to be very low (median 5 μg/L, versus 32 μg/L for the Quebec study) and not associated with IQ scores in the overall group of children ($n = 274$). In fact, sex-stratified analysis showed that higher water manganese levels were rather associated with better Performance IQ scores in boys, and there was no significant association in girls. However, further analysis showed that higher concentrations of manganese in nails (another biomarker of exposure) were significantly associated with worse Performance IQ scores in girls (Bouchard et al., 2018).

Despite the relatively common occurrences of elevated concentrations of manganese in water, its level in drinking water is rarely regulated. The U.S. EPA (2004) has set a secondary standard for manganese of 50 μg/L for aesthetic reasons (color, staining and taste) and a non-regulatory health advisory for lifetime exposure of 300 μg/L in drinking water. The WHO health-based value of 400 μg/L has been discontinued while asserting that such elevated manganese levels are not normally found in drinking-water (WHO, 2011), despite evidence to the contrary (Frisbie et al., 2012). Currently, there is no official health-based guideline in Canada, but recently a maximum acceptable concentration of 100 μg/L was proposed based on neurological effects observed in neonatal rats (Health Canada, 2016). An analysis based on human data would be preferable to issue recommendations of a maximum allowable drinking water manganese level.

Benchmark dose (BMD) modeling is widely accepted as the best approach for dose-response analysis in human health risk assessment (European Food Safety Authority (EFSA) Scientific Committee, 2017). The BMD is the dose that produces a pre-specified change in an adverse response; this pre-specified change is the benchmark response (BMR). In addition to the BMD, the lower bound of the one-sided 95% confidence interval (i.e., BMDL) is also calculated, and can be used to derive a criterion for regulatory purposes that provides a margin of safety to ensure protection of the most sensitive individuals. Recently, Shao and Shapiro (2018) have made available a tool to carry out this analysis in a multi-step probabilistic framework. The Bayesian Benchmark Dose Analysis System (BBMD) is capable of analyzing epidemiological exposure-response data (e.g., unique exposure level and response for each subject) and provides distributional estimates for BMD and other important metrics in dose-response assessment.

Studies suggest that a maximum acceptable concentration for manganese in drinking water should be set to protect children, the most vulnerable population, from manganese neurotoxicity. Hence, the objective of the present study was to use pooled data from our two previously conducted cross-sectional studies (Bouchard et al., 2011, 2018) to estimate the concentration of manganese in drinking water associated with three different levels of reduction in Performance IQ (i.e., decrease of 1%, 2%, and 5%) using the BBMD approach. These BMRs are similar to those in previous benchmark dose analyses for neurotoxicants (Budtz-Jorgensen et al., 2013; Jacobson et al., 2002; U.S. National Research Council, 2000). For the present pooled analysis, we focused on Performance IQ as the outcome of interest since it was most reliably associated with manganese exposure in previous studies (Bouchard et al., 2011, 2018; Wasserman et al., 2006). This analysis could guide decision-makers responsible for developing standards for the presence of manganese in drinking water.

2. Methods

2.1. Study populations

This pooled analysis combines data from our two cross-sectional studies conducted in Canada. The main objective of both studies was to examine the association between manganese concentration in drinking water and cognition in children. The first study, led by Bouchard et al. (2011) from June 2007 to June 2009, recruited 375 children from the province of Quebec. The second study, also led by Bouchard et al. (2018), conducted between April 2012 and April 2014, included 274 children from the province of New Brunswick. Communities using groundwater wells were targeted for inclusion in these studies since elevated manganese levels much more common in groundwater than in surface water (i.e. lakes and rivers). We identified 8 communities in Quebec, and 10 communities in New Brunswick where groundwater was used for human consumption. By design all study participants lived in a house supplied by well-water, ether from a domestic (private) well or from a public well that supplied a municipal water system. In the Quebec study, 50% of participants lived in a house supplied by a municipal aqueduct (public well) and the remaining participants lived in a house supplied by a domestic well. In the New Brunswick study, all participants lived in a house supplied by a domestic well.

Children were recruited through the primary schools located in these municipalities. After authorization from the school district, the study was presented to the principals and teachers of the selected schools, who agreed to distribute recruiting letters to all children ages 6–13 years to bring home to their parents. In both studies, we only enrolled participants who had been living in their current house for more than four months. For the present analysis, we excluded 19 children because of barriers to cognitive testing (e.g., major neurological problems, not collaborating). The analytical sample was composed of 630 children, including 302 boys (47.9%) and 328 girls (52.1%), ages 5.9 to 13.7 years. The distribution of sex and age were similar between the Quebec and New Brunswick studies. However, the participants from the New Brunswick had higher socioeconomic status, as indicated by significantly higher maternal education and family income (Table S1).

The required institutional human research ethics boards approved both studies. We obtained signed informed consent from the parents and verbal consent from the children prior to data collection.

2.2. Measurement of manganese in tap water

We visited the home of each participant to sample tap water and to collect information on the use of tap water in both studies. We collected a water sample from the kitchen tap using a standardized procedure (Van den Hoven and Slaats, 2006). This includes letting the water run for 5 mins, closing the tap for 30 mins, and collecting the first draw. We acidified and stored samples at 4 °C. We used inductively coupled plasma-mass spectrometry (ICP-MS) to measure manganese, as well as other metals (Cr, Fe, Co, Ni, Cu, Zn, As, Cd, Pb). Only one sample had a manganese concentration below the detection limit (i.e., 0.1 μg/L). We used method blanks as well as field blanks, verification check standards, and sample replicates for quality assurance.

2.3. IQ assessment

In the Quebec study, we used the Wechsler Abbreviated Intelligence Scale for Children (WASI) (Wechsler, 1999), which consists of four subtests (Block Design, Matrix Reasoning, Similarities, and Vocabulary). In the New Brunswick study, we used these same subtests, but from the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2003). For both studies, this yielded a Performance and a Verbal IQ score. We tested children using the French Canadian versions of the WISC-IV (Wechsler, 2005) and WASI. In both studies, a senior psychologist trained the testers (graduate students in psychology) until full compliance with the test manuals. IQ testers were blind to the exposure status of children. Children completed the IQ tests in a room free of distraction in community centers or schools over the weekend to ensure that children were well rested to perform at their best.

For the present pooled analysis, we focused on Performance IQ as the outcome of interest. Since we used slightly different instruments to assess cognition in the two studies, we applied the following procedure to harmonize Performance IQ scores for the pooled analysis: i) We converted WASI standardized scores for the subtests Block Design and Matrix Reasoning into equivalent WISC-IV standardized scores using the equivalency table in the manual (Wechsler, 1999). ii) We summed these standardized scores for Block Design and Matrix Reasoning to compute Performance IQ scores, using the Tellegen and Briggs' formula (Sattler, 2001) and the WISC-IV subtest correlations reported in the manual (Wechsler, 2003).

2.4. Adjustment of performance IQ scores for potential confounders

Prior to conducting the BMC analysis, we adjusted Performance IQ scores for variables that could be potential confounders or important determinants of scores, considering the following variables: maternal education (high school or less, at least some college, undergraduate degree, graduate degree), maternal nonverbal intelligence as measured by Raven's Progressive Matrices Test (tertiles), household income (9 categories, used as a continuous variable), Home Observation Measurement of the Environment (HOME) score (tertiles), child age (months), birth weight (grams), IQ tester (8 psychometricians), and water concentrations of iron, lead and arsenic. We used the following strategy to select variables for IQ adjustment. First, we retained variables associated with both Performance and water manganese concentration ($\log_{10}$-transformed) at $p < 0.2$ (household income and IQ tester were selected). Second, the remaining variables were individually added in the model with the two previous covariates and selected if the association estimates changed by > 10% (maternal education and maternal nonverbal intelligence were selected).

We ran a multivariable regression analysis on Performance IQ scores and the above-mentioned variables, saved the unstandardized residuals, and added the mean value of Performance IQ to bring scores to the usual IQ scale. This method was used in a previous study also aimed at calculating a benchmark-dose for prenatal exposure to PCBs (Jacobson et al., 2002). We used SPSS Version 25.0 to carry out these analyses (IBM Corporation, USA).

2.5. Determining BMCs and BMCLs for manganese in drinking water

The benchmark concentration of manganese in drinking water in relation with predefined Performance IQ scores deficits was estimated using the BBMD, a web-based tool used for probabilistic risk assessment available at (Indiana University School of Public Health, USA). Benchmark concentrations (BMCs) and their lower bounds (BMCLs), defined as the median and 5th percentile of the posterior sample in BBMD respectively, for different levels of adverse response were estimated, i.e., BMRs corresponding to a reduction in 1%, 2% and 5% of Performance IQ points.

Concentration-response data were modeled using seven continuous model functions (i.e., linear, Hill, power, exponential 2, 3, 4, and 5). Because of inadequate performance in BMC estimation for relatively flat concentration-response relationship, the Michaelis-Menten model was excluded from the model suite for BMC analysis. We modeled the response data using the assumption that Performance IQ scores were normally distributed. Markov Chain Monte Carlo (MCMC) algorithm was used to generate posterior sample of model parameters to form the distributional estimates of the parameters. Default settings for the MCMC algorithm (one chain with 30,000 samples with the first half discarded as burn-in) were applied as this is adequate for most dose-response data (Shao and Shapiro, 2018). As recommended by the U.S. EPA, the power parameter in the Hill, power and exponential 3 and exponential 5 models was restricted to ≥ 1 to avoid extremely steep slope in the low concentration region (U.S. EPA, 2012). Background manganese exposure was set to 0 μg/L for BMC calculation since a sizable fraction of our sample had such low manganese levels in water (i.e., 18.6% of water samples had a concentration below 1 μg/L).

Various indicators were computed to verify the adequacy of the MCMC settings and model fitting results. First, $\hat{r}$ and N_effective values were used to evaluate the quality of MCMC sampling (i.e., convergence and effective sample size, respectively). Then, the posterior predictive *p*-value (PPP) value was used to assess model fit. A PPP value between 0.05 and 0.95 generally suggests adequate fit (Shao and Shapiro, 2018). Third, based on how well the models fit the data, weights were computed for each model, which can be used to compare the models and quantifies model uncertainty. A model-averaged benchmark concentration estimation was finally computed based on the integration of the distribution of BMC estimated from each model by considering their weights. A model with greater weight (better overall fit) would have greater bearing on the calculation of the model-averaged BMC.

Finally, we ran analyses on the entire group of children and on sex-stratified samples since previous studies on manganese exposure showed differential associations for boys and girls (Bauer et al., 2017; Bouchard et al., 2018; Oulhote et al., 2014a; Riojas-Rodriguez et al., 2010).

Table 1
Descriptive statistics on household water manganese concentrations (μg/L) and Performance IQ in relation with family and child characteristics.

Characteristic	n	(%)	GM water manganese	(GSD)	p-Value	Performance IQ (SD)	p-Value
Study					< 0.0001		< 0.0001
Quebec	371	(58.9)	20.2	(2.6)		106.5 (14.2)	
New Brunswick	259	(41.1)	6.2	(3.0)		100.5 (13.9)	
Age (years)					0.234		0.239
5–8 years	199	(31.6)	14.1	(3.0)		102.9 (14.6)	
8.1–11 years	296	(47.0)	13.2	(2.7)		105.1 (14.7)	
11.1–14 years	135	(21.4)	9.1	(2.7)		103.5 (13.4)	
Sex					0.241		0.086
Boy	302	(47.9)	11.1	(2.9)		105.1 (15.4)	
Girl	328	(52.1)	13.9	(2.9)		103.1 (13.4)	
HOME score					0.793		0.266
Low (1–3)	315	(50.0)	12.1	(2.8)		104.6 (14.1)	
Medium (4)	230	(36.5)	13.5	(3.0)		102.9 (14.8)	
High (5+)	85	(13.5)	11.2	(2.9)		105.3 (14.2)	
Maternal education					0.245		< 0.0001
High school	112	(17.8)	16.4	(1.1)		107.8 (14.4)	
College/technical	278	(44.1)	12.6	(2.1)		106.9 (14.5)	
Undergraduate	204	(32.4)	10.6	(1.1)		103.7 (13.8)	
Graduate	36	(5.7)	5.6	(1.2)		98.5 (14.2)	
Maternal intelligence					0.212		< 0.0001
Lowest tertile	222	(35.2)	15.0	(3.2)		99.8 (14.0)	
Middle tertile	244	(38.7)	11.4	(2.9)		104.2 (13.6)	
Highest tertile	164	(26.0)	8.9	(2.6)		109.8 (14.2)	
Family income (CAN$)					0.002		0.009
< 50k	205	(32.5)	19.6	(2.6)		101.5 (14.9)	
50k–80k	228	(36.2)	12.2	(2.8)		105.4 (13.7)	
> 80k	197	(31.3)	7.0	(2.3)		105.1 (14.4)	

GM: geometric mean; GSD: geometric standard deviation.

3. Results

Table 1 presents descriptive statistics on tap water manganese concentrations and Performance IQ of the pooled sample of 630 children. The pooled sample included more children from Quebec than New Brunswick (59% and 41%, respectively). The proportion of boys in the pooled sample was similar to that of girls (48% and 52%, respectively). The average age was 9.3 years, ranging from 5.9 to 13.7 years. Maternal education was high with nearly 83% of the mothers attaining some college or university education. Finally, 80% of children had been living in their current house for over three years; only 6% of children lived in their current house for less than a year.

All study participants lived in a house supplied by well-water, by design. For the majority of participants (69%), water came from a domestic (private) well and for the remaining (31%) it came from a public well. Household tap water manganese concentrations in the pooled sample ranged from 0.01 μg/L to 2701 μg/L with a geometric mean of 12.3 μg/L and an arithmetic mean of 84.8 μg/L. Thirty-six percent of children (103 boys and 123 girls) were exposed to tap water manganese levels above the aesthetic guidelines of 50 μg/L used by Health Canada and the U.S. EPA. In addition, 4% (8 boys and 17 girls) were exposed to levels higher than 400 μg/L, which is the former health-based WHO guideline. For these 25 children, we phoned parents to inform them of their tap water manganese concentration and provided written information on options for treatments to reduce manganese levels in tap water.

Among different family and child characteristics, only family income was significantly associated with water manganese concentrations ($p = 0.002$), water manganese being higher in households with lower income (Table 1). Water manganese concentrations were not associated with characteristics such as child age, sex, HOME score, maternal nonverbal intelligence, or maternal education. Water manganese concentrations were higher in the Quebec study than in the New Brunswick (i.e., geometric mean of 20.2 μg/L and 6.2 μg/L, respectively).

The other elements measured in water samples were found in low concentrations (Supplemental Material, Table S2). For instance, the median concentration of arsenic (As) was 4.4 μg/L and the 95th percentile was 7.6 μg/L; 3% of samples over the health-based guideline of 10 μg/L. For lead (Pb), the median concentration was 0.4 μg/L and the 95th percentile was 2.8 μg/L, with only 0.3% of samples over the health-based guideline of 10 μg/L.

Significantly higher Performance IQ scores were observed with higher maternal education, maternal intelligence, and family income (Table 1). Scores were significantly higher in the Quebec study than in the New Brunswick study. Performance IQ scores were slightly higher in boys than girls, but scores were not associated with children's age and HOME scores. Furthermore, concentrations of tap water arsenic, lead, and iron were not associated with Performance IQ scores (all at $p > 0.2$).

After adjusting for covariates (i.e., maternal education, maternal intelligence, household income, and IQ tester), a regression analysis showed that higher manganese concentration in water was significantly associated with lower Performance IQ (β for a 10 μg/L increase in concentration: −0.08, 95% confidence intervals [95% CIs]: −0.14, −0.02; $p = 0.006$). We added an interaction term for sex × water manganese in this model and the p-value was not significant ($p = 0.56$). In sex-stratified analyses, higher manganese levels were associated with lower scores for both sexes, and the association was significant in girls (β: −0.08, 95% CIs: −0.15, −0.02; $p = 0.021$) but not in boys (β: −0.08, 95% CIs: −0.18, 0.03; $p = 0.15$). Furthermore, we introduced a term for the interaction between the study (Quebec or New Brunswick study) and water manganese levels and it was not significant ($p = 0.515$) suggesting similar associations between manganese and IQ scores between studies.

Table 2 presents the estimated individual models and model-averaged BMCs and BMCLs for BMRs of 1%, 2% and 5% reduction in Performance IQ scores (previously adjusted for confounders), for the sex-aggregated and sex-stratified data. As expected, BMCs and BMCLs increased with increasing BMR. The PPP values were all within the range from 0.05 to 0.95, indicating that all models had adequate fit to the data. The fact that the majority of $\hat{r}$ values were equal to 1 with a maximum of 1.091 suggests that the MCMC sampling converged well. Some complex models (i.e., models with more parameters) had

Table 2
Water manganese BMCs and BMCLs (μg/L) for the total and sex-stratified sample based on benchmark response of 1, 2 and 5% reduction in Performance IQ scores.

Model	Weight (%)	PPP	$\hat{r}$	N_eff	↓ 1% performance IQ		↓ 2% performance IQ		↓ 5% performance IQ	
					BMC	BMCL	BMC	BMCL	BMC	BMCL
Both sexes (n = 630)										
Linear	44.5	0.488	1.000	7111	141	89	282	177	705	443
Power	0.7	0.492	1.000	8398	803	137	1138	261	1800	597
Hill	0.0	0.508	1.000	382	6898	124	7999	211	10,462	490
Exponential 2	49.8	0.492	1.000	7329	127	79	256	158	651	402
Exponential 3	0.8	0.486	1.000	2202	513	121	779	231	1369	535
Exponential 4	4.1	0.491	1.000	6864	65	20	142	49	476	224
Exponential 5	0.1	0.639	1.091	17	161	68	209	109	453	254
Model-average	–	–	–	–	133	78	266	156	676	406
Boys (n = 302)										
Linear	44.1	0.484	1.000	4735	171	76	342	153	855	381
Power	4.9	0.487	1.000	2434	1240	380	1361	546	1531	872
Hill	0.2	0.482	1.000	816	7111	556	8181	692	9987	922
Exponential 2	43.6	0.493	1.000	5570	167	73	335	148	851	375
Exponential 3	4.7	0.494	1.000	1722	1205	377	1321	534	1492	836
Exponential 4	2.3	0.517	1.033	105	118	16	290	48	939	346
Exponential 5	0.2	0.489	1.000	513	572	29	714	161	939	440
Model-average	–	–	–	–	185	75	375	153	935	386
Girls (n = 328)										
Linear	13.7	0.491	1.000	7425	131	81	263	161	657	403
Power	0.1	0.485	1.002	889	1795	134	2045	254	2393	588
Hill	10.0	0.491	1.007	454	92	42	104	61	157	91
Exponential 2	17.8	0.489	1.000	7008	110	66	222	133	563	337
Exponential 3	0.2	0.476	1.000	755	1441	104	1736	201	2189	475
Exponential 4	35.0	0.493	1.000	10,561	18	7	39	15	139	56
Exponential 5	23.2	0.483	1.000	1272	82	43	91	54	109	77
Model-average	–	–	–	–	78	9	95	21	192	74

PPP, posterior p-value; $\hat{r}$, convergence; N_eff, effective sample size for MCMC sample; BMC, benchmark concentration; BMCL, lower bound of benchmark concentration.

relatively small effective sample size, consistent with findings in Shao and Shapiro (2018), but those models had limited impact on model-averaged estimates due to small weights.

Table 2 also shows that the estimated BMCs and BMCLs varied greatly between the different exposure-response models. For instance, BMCs for a BMR of 1% varied between 65 μg/L (exponential 4) and 6898 μg/L (Hill) in analyses including both sexes. However, model weights indicate that the linear and exponential 2 models had much larger loading than the five other models (i.e., weights of 44.5 and 49.8%, respectively), which is not only because both models have a relatively good fit to the data, but also because they only have two parameters, while others have three or four parameters. Focusing on these two models with the highest weights, we observed that they yielded similar BMCs and BMCLs. For a BMR of 1%, the BMC was 141 μg/L for the linear model and 127 μg/L for the exponential 2 model (BMCLs, 89 and 79 μg/L, respectively). For a BMR of 2%, the BMC was 282 μg/L for the linear model and 256 μg/L for the exponential 2 model (BMCLs, 177 and 158 μg/L, respectively). For a BMR of 5%, the BMC was 705 μg/L for the linear model and 651 μg/L for the exponential 2 model (BMCLs, 443 and 402 μg/L, respectively). Finally, the model-averaged estimated yielded the following BMCs for BMRs of 1, 2, and 5%: 133, 266, and 676 μg/L (BMCLs, 78, 156, 406 μg/L, respectively). The full distributional estimates are presented in Supplemental Material (Table S4).

Sex-stratified models for boys also showed that linear and exponential 2 models had the highest weights. BMCs from linear models were very similar to those from exponential 2 models (e.g., for a BMR of 1%, 171 and 167 μg/L, respectively). Analyses including only boys resulted in BMCs slightly higher than those including both sexes. Model-averaged estimates for boys yielded the following BMCs for BMRs of 1, 2, and 5%: 185, 375, and 935 μg/L respectively (BMCLs, 75, 153, 386 μg/L, respectively).

Sex-stratified models for girls had a different repartition of weights, with exponential 4 having the largest weight (35.0%), following by exponential 5 (23.2%), exponential 2 (17.8%), linear (13.7), Hill (10.0%), exponential 3 and power (0.2 and 0.1%, respectively). Model-averaged estimates for girls yielded the following BMCs for BMRs of 1, 2, and 5%: 78, 95, and 192 μg/L respectively (BMCLs, 9, 21, 74 μg/L, respectively). Hence, BMCs and BMCLs for girls were much lower than those for boys, or than those for both sexes modeled together.

Finally, we ran a sensitivity analysis excluding children exposed to water manganese concentrations above the 99th percentile, i.e., above 1000 μg/L (n = 6 children). The resulting BMCs and BMCLs were lower than in the main analysis (Supplemental Material, Table S5). In the model for a 1% reduction in Performance IQ, this sensitivity analysis yielded a BMC of 106 and BMCL of 60 μg/L (compared with 133 and 78 μg/L in the main analysis). For a 2% reduction in IQ, it yielded a BMC of 214 and BMCL of 121 μg/L (compared with 266 and 156 μg/L in the main analysis). The analysis for a 5% reduction in IQ yielded a BMC of 541 and BMCL of 311 μg/L (compared with 676 and 406 μg/L for the main analysis). The full distributional estimates are presented in Table S6.

4. Discussion

In the present study, we pooled data from our two cross-sectional epidemiological studies whose original aim was to examine the association between water manganese and cognition in school-age children consuming well water. In this pooled sample of 630 children, higher manganese concentration in water was significantly associated with lower Performance IQ scores after adjusting for covariates, supporting the relevance of conducting a benchmark concentration analyses to identify exposure levels associated with pre-defined levels of deficits in cognition. An interaction analysis indicated homogeneity in the association between water manganese and IQ scores between studies, further supporting pooled analysis.

The present analysis has some limitations. Since the data were cross-sectional, it is not clear whether cognitive deficits could be the result of cumulated exposure or, possibly, exposure during a critical developmental period. In particular, infants and young children could be at elevated risk because of increased absorption resulting from their underdeveloped homeostatic mechanisms (Winder, 2010). Although complete longitudinal data on exposure and development would be ideal, the limited information of exposure to manganese in early life does not threaten the validity of the association reported here. It should also be noted that the usual concern of reverse causality for cross-sectional studies is extremely unlikely to operate here. Furthermore, although we measured manganese concentration at only one time point, this measure can be reasonably argued to be representative of long-term exposure levels. First, we carried out repeated water sampling in a subsample of houses and measured manganese several times over one to three years, which resulted in intraclass correlations above 0.90 (Barbeau et al., 2011; Bouchard et al., 2011, 2018). Second, 80% of children in this pooled sample had been living in the same house for more than three years, hence, had been consuming water from the same well. We based our estimate of exposure to water manganese on the concentration measured in tap water at home, which might introduce some misclassification of exposure since children may consume water from other sources. However, the result from exposure misclassification is likely to be non-differential and would bias estimates towards the null. Also, other sources of exposure certainly contribute to the total manganese exposure, but again, this should not threaten the validity of the results reported here. Iron status is potentially important factor to consider when studying manganese neurotoxicity, since greater blood manganese levels have been observed in individuals with lower iron status (Finley et al., 1994; Kim and Lee, 2011; Oulhote et al., 2014b). However, iron deficiency is uncommon in Canadian children, with only 3% of those ages 6–11 years having insufficient hemoglobin (Cooper et al., 2012). Some polymorphisms could also confer vulnerability to manganese exposure (Wahlberg et al., 2018). Variability in response to toxics is to be expected, and use of the BMCL (rather than the BMC) for setting regulatory standards may account for individual differences in sensitivity.

The use of BBMD provided results on the levels of water manganese concentration associated with reduction in pre-defined deficits in Performance IQ scores. We fitted seven different models to the data all models had an adequate fit. Two concentration-response models with simple format (i.e., linear and exponential 2) had the highest model weights and produced consistent estimates. For a BMR of 1%, the BMC was 141 μg/L for the linear model and 127 μg/L for the exponential 2 model (BMCLs, 89 and 79 μg/L, respectively). However, benchmark concentration estimates resulting from model-averaged analysis, rather than specific model analysis, are recommended for use in regulatory standards (EFSA, 2017). Furthermore, the lower bound of the estimate is usually considered the most appropriate for setting regulatory standards because it provides protection for sensitive individuals (EFSA, 2017).

The magnitude of excess risk considered acceptable has substantial impact on the results of a benchmark concentration analysis. This consideration, however, depends on societal values, the level of scientific evidence, and applicability. In the present study, benchmark responses of 1% and 2% IQ point reduction were similar to those in previous benchmark dose analyses for lead (Budtz-Jorgensen et al., 2013) and polychlorinated biphenyls (PCBs) (Jacobson et al., 2002). We also included a BMR of 5% reduction in Performance IQ, similar to other studies on PCBs (Jacobson et al., 2002) and methylmercury (U.S. National Research Council, 2000). However, this magnitude of cognitive deficit would be unacceptably large to be deemed protective of children's neurodevelopment. The crucial importance of optimal cognitive functioning for several long-term outcomes, including educational attainment, lifetime earnings (Grosse et al., 2002), and incidence of cardio-vascular disease (Batty et al., 2010), should be considered when choosing the acceptable excess risk.

Currently, there are few guidelines to limit the concentration of manganese in drinking water. The WHO had set a maximum of 400 μg/L for manganese but it was dropped in the latest edition of its guideline document for drinking-water quality (WHO, 2011). The U.S. EPA has a non-regulatory health-based guideline of 300 μg/L (U.S. EPA, 2004). These concentrations are close to the level associated with a reduction of 5% of Performance IQ scores, since the model-averaged BMCL in the sex-aggregated analysis was 406 μg/L. Health Canada recently proposed a health-based guideline of 100 μg/L (Health Canada, 2016), which is closer to the concentration associated with a 1% reduction in Performance IQ scores, i.e., a BMC of 133 μg/L and a BMCL of 78 μg/L for the model-averaged analysis.

Our findings suggest the relevance of considering sex-related differences when estimating maximum concentration limits for manganese in drinking water. The BMCLs for girls were quite low (e.g., 9 μg/L for a reduction of 1% IQ point), possibly reflecting increased sensitivity in girls. The low BMCLs are also a consequence of the larger confidence intervals resulting from the smaller sample sizes in sex-stratified analyses. Numerous studies have noted a differential association between boys and girls in the associations between environmental manganese exposure and neurodevelopment (Bauer et al., 2017; Bouchard et al., 2018; Chiu et al., 2017; Hernandez-Bonilla et al., 2011; Hernandez-Bonilla et al., 2016; Menezes-Filho et al., 2014; Riojas-Rodriguez et al., 2010; Torres-Agustin et al., 2013). The reasons are not well understood, but kinetics may play a role since higher absorption rates have been measured in women than in men for a given intake of ingested manganese (Finley et al., 1994). Furthermore, our analysis of population survey data from Canada showed that girls and women had significantly higher blood manganese than boys and men (Oulhote et al., 2014b).

Elevated manganese concentrations in ground water are common in several countries worldwide (Frisbie et al., 2012). In the U.S., approximately 115 million people, more one third of the population, depends on groundwater for drinking water (U.S. Geological Survey, 2019). The distribution of manganese levels in well water cannot be inferred from our studies since sampling was not meant to be representative of the population. Indeed, our participant recruitment strategy aimed ensuring adequate exposure to contrast for examining exposure-response relation for a wide range of exposure levels. A more valid source of data on the distribution of manganese levels in well water is available for the U.S. (but not Canada) through the National Water Information System database. Table 3 presents the distribution of concentrations in 11,965 domestic wells and shows manganese levels above the concentrations associated with a 1% or 2% reductions in Performance IQ scores (data table provided by Peter McMahon from the

Table 3
Distribution of water manganese concentrations in the high range of concentrations, i.e., above the 80th percentile, in 11,965 domestic wells sampled from 1988 to 2017 (National Water Information System [NWIS], United States' Geological Survey [USGS]). This table was provided by Peter McMahon, USGS.

Percentile distribution	Manganese in domestic well water (μg/L)
99	1264
98	850
97	651
96	498
95	414
94	354
93	310
92	270
91	236
90	210
89	180
88	160
87	148
86	130
85	120
80	71.5

USGS). These data show that approximately 20% of domestic wells had manganese levels higher than those corresponding to the BMCL for a 1% decrease in Performance IQ (i.e., 78 μg/L), 12–13% for a decrease of 2% (i.e., 156 μg/L), and 5–6% for a decrease of 5% (i.e., 406 μg/L). Furthermore, according to a recent analysis by U.S. Geological Commission scientists, approximately 2.6 million individuals in the U.S. potentially consume groundwater with manganese concentration above 300 μg/L (McMahon et al., 2019).

5. Conclusion

The present analysis has several strengths, including a reasonably large sample size and reduction of confounding, and we believe that the results can guide decision-makers to set a maximum acceptable concentration for manganese in drinking water to protect children, a group of the population that is particularly vulnerable to manganese neurotoxicity. Given the potential importance of this problem for public health, further studies should examine associations between manganese exposure from drinking water and neurodevelopment.

Declaration of Competing Interest

The authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.083.

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