TOX/2018/02

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

First draft statement on the potential risks from manganese in the diets of infants aged 0-12 months and children aged 1 to 5 years.

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government dietary recommendations for infants and young children. The SACN is examining the nutritional basis for the advice. The COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children. The reviews will identify new evidence that has emerged since the Government recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. A scoping paper (TOX/2015/32), highlighting some of the chemicals for possible consideration for the diet of young children aged 1-5 years was discussed by the COT in October 2015. Members concluded that a review on the potential risks from manganese in the diet of young children aged 1-5 years should be completed.

3. The secretariat carried out a review of the literature which was presented at the meeting in December 2017. Members comments have been taken into account and a draft statement has been prepared for discussion at the current meeting which can be found in annex 1 of this paper.

Secretariat
January 2018

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

First draft statement on the potential risks from manganese in the diets of infants aged 0-12 months and children aged 1 to 5 years.

Introduction

4. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government dietary recommendations for infants and young children. The SACN is examining the nutritional basis for the advice. The COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children. The reviews will identify new evidence that has emerged since the Government recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

5. The UK population's exposure to manganese was measured in the 2000 Total Diet Study (TDS). The dietary exposure of adults to manganese for mean and high level consumers was respectively 5.2 and 9.2 mg/day. The COT reviewed the results from the 2000 TDS and concluded that the estimated total dietary intake of manganese is unlikely to pose a risk to health in normal, healthy individuals[1]. More recently, the Food Standards Agency completed a survey of 15 elements, including manganese, in infant formula, commercial infant foods and other foods. From the measured levels of manganese, the Committee concluded that the current estimated dietary exposures to manganese were not of toxicological concern[2].

6. No Reference Nutrient Intake (RNI) has been set for manganese as there were limited data on deficiency. In 1993, the EU Scientific Committee on Food (SCF) considered a safe and adequate intake to be 1-10 mg/person/day.

Background

7. Manganese is found naturally in oxidation states Mn^{2+}, Mn^{3+} and Mn^{4+} in the environment, and can also be released as a result of anthropogenic activity. The most biologically active oxidation states of manganese are Mn^{2+} and Mn^{3+} (EVM 2003).

8. Manganese is an essential micronutrient in the human diet. It is a necessary component of a number of enzymes and activates others such as glycosyl transferases. Manganese deficiency has only been documented under experimental conditions where decreased levels of cholesterol and clotting proteins were

[1] Available at: https://cot.food.gov.uk/sites/default/files/cot/cotstatements2004metals.pdf
[2] Available at: https://cot.food.gov.uk/cot-meetings/cotmeets/cot-meeting-5-july-2016

recorded. Black hair was found to redden, fingernail growth slowed and scaly dermatitis was observed (EVM, 2003).

9. A chronic excess of manganese has been found to produce a range of neurological symptoms in humans which combine, in severe cases to form a Parkinson disease-like syndrome called Manganism. Primary symptoms include reduced response speed, intellectual deficits, mood changes and compulsive behaviour in the initial stages to more prominent irreversible extrapyramidal dysfunction in more severe cases. Cases of Manganism are primarily associated with occupational exposure through mining and welding where inhalation of atmospheric manganese is the primary route of exposure. Brain scans have shown injury in the basal ganglia of the brain in patients with Manganism which is consistent with rat studies showing loss of neurons in the substantia nigra after oral exposure to elevated manganese for 18 months (paper suggests gavage, but not clear) (Roth, 2006).

Expert Opinions on Health-Based Guidance Values (HBGVs)

10. The Expert Group on Vitamins and Minerals (EVM) looked in detail at the metabolism of manganese and the effects of excess manganese in 2003[3]. Further information can be found in the background document prepared for the EVM[4]. The EVM concluded that there were insufficient data to set a Safe Upper Level (SUL) for manganese but for guidance they indicated that a level of 0.2 mg/kg bw/day total manganese would be unlikely to cause adverse effects in adults based on the NOAEL from a large retrospective cohort study. The EVM noted that older populations may be more sensitive to the neurological effects of manganese. Information published since the EVM opinion of 2003 was obtained through a literature search in Pubmed using the search terms noted in appendix 1. This information has been included in this statement.

11. In 2006, the European Food Safety Authority (EFSA) published an opinion on the tolerable upper intake levels of vitamins and minerals. For manganese, they were unable to set a tolerable upper level (TUL) because of a lack of data.

12. The WHO derived a TDI of 60 µg/kg body weight/day in the Guidelines for Drinking Water Quality (WHO, 2011). This was based on the upper range value of manganese intake of 11 mg/day, identified using dietary surveys, at which there were considered to be no observed adverse effects. An uncertainty factor of 3 was applied to take into consideration the possible increased bioavailability of manganese from water. No information was provided on how these reference doses were set in relation to speciation. Based on this TDI, the WHO set a health-based guidance value for water of 400 µg/L.

[3] Available at: https://cot.food.gov.uk/sites/default/files/cot/vitmin2003.pdf
[4] Available at: http://webarchive.nationalarchives.gov.uk/20110911090542/http://www.food.gov.uk/multimedia/pdfs/evm9922p.pdf

13. A number of HBGVs for chronic exposure through air have been identified: USEPA (0.05 µg Mn/m^3), ATSDR (0.04 µg Mn/m^3), and the World Health Organization (WHO) (0.15 µg Mn/m^3).

Manganese exposures in infants aged 0-12 months and young children aged 1-5 years

Sources of manganese exposure

Human breast milk

14. From a survey of 82 French lactating mothers who provided milk samples each day for the first 7 days postpartum, manganese concentrations of breast milk were found to peak at day 2 postpartum (calculated to be 12.0 µg/L +/- 5.6 µg/L) and decline to 3.4 µg/L +/- 1.6 µg/L at 6 days postpartum (Arnaud & Favier, 1995).

15. Lactating mothers aged 19-40 from 6 regions of Italy provided milk samples at the end of the first month of breastfeeding. Results for manganese varied between regions with the highest level found in Verona (56.6 ng/ml SD 3.9) and the lowest levels found in Turin (13.8 ng/ml) SD 0.6). Pooled samples were also analysed for mothers below 30 years old and those above 30 years old. No age related differences were found in manganese concentrations between the two groups (Bocca et al, 2000).

16. A median concentration of 6.3 µg/kg is reported for manganese in breast milk (Krachler et al, 2000). This value was derived from the pooled samples of breast milk donated by 27 healthy mothers in Austria.

17. According to EFSA, average manganese concentrations in breast milk range from <0.1 µg/L to 40 µg/L (EFSA, 2013). The maximum value of 40 µg/L reported by EFSA was used in the exposure assessments from this source.

Infant formulae and food

18. Levels of manganese have recently been measured in an FSA survey of metals and other elements in infant formulae and food (FSA, 2016a) and in the composite food samples of the 2014 Total Diet Study (TDS) (FSA, 2016b).

Drinking water

19. Manganese is present in soil and surface waters and its concentration can vary seasonally. Manganese can cause staining of clothes at levels below those that may be expected to cause adverse health effects and therefore the maximal level permissible in drinking water is set below any expected HBGV.

20. Levels of manganese in drinking water in 2016/2017 from England and Wales, Northern Ireland and Scotland were provided by the Drinking Water Inspectorate (DWI), Northern Ireland Water and the Drinking Water Quality Regulator (DWQR) for Scotland, respectively. Median and 97.5th percentile values calculated from these data are shown in Table 2. These values have been used to

calculate exposures to manganese from drinking water in combination with exposures from food.

Table 1. Median and 97.5th percentile concentrations (µg/L) of Manganese in water across the UK for 2014/2015

Country	Number of samples	Limit of Detection (µg/L)	Median concentration (µg/L)	97.5th Percentile concentration (µg/L)
England and Wales	16140	0.8-1.0	1	4.5
Northern Ireland	1896	0.05	**1.4**	14.9
Scotland	5068	1	1.1	**15**

* The DWI noted that the water companies had reported a range of LODs that varied with the analytical method used, and clarified that the relevant drinking water regulations specify that the LOD must not be more than 10% of the prescribed value (0.05 µg/L for manganese)

Environmental

Dust and soil

21. Manganese is present at about 550–600 mg/kg in the upper continental crust, with higher levels in basic igneous rocks (1500 mg/kg) than in granites (400 mg/kg) and low levels in sandstones (100 mg/kg). Concentrations in greywacke, shale and limestone are generally in the 700–850 mg/kg range (BGS, 2012). In the absence of specific UK data on household levels of indoor dust, the median value of 90 mg/kg and the highest 90th percentile concentration value of 225 mg/kg for manganese in soil from the Defra-commissioned BGS project have been used to estimate exposures to soil and dust in this assessment.

Air

22. Data from 47 air sampling sites across the UK have been collected by Defra (https://uk-air.defra.gov.uk/data/non-auto-data?uka_id=UKA00168&view=data&network=metals&year=2016&pollutant=262#view).The data for 2016 have yielded lowest and highest median values of 0.73 and 85 and lowest and highest 99th percentiles of 1.6 and 155 ng manganese/m^3 across the sites

Exposure assessment

23. Consumption data (on a bodyweight basis) from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and from years 1-4 of the National Diet and Nutrition Survey (NDNS) (Bates et al., 2014) have been used for the estimation of dietary exposures for ages 4 to 18 months, and 18 to 60 months

respectively. Bodyweight data used in the estimation of other manganese exposures are shown in Table 2 below.

24. Thorough exposure assessments have been performed for the dietary sources of exposure to manganese. The assessments for the non-dietary sources of exposure (i.e. air, dust and soil) have been included to give a more holistic view of exposures, but are not as thorough as the focus of this statement is the diet of infants and young children.

Table 2. Average bodyweights used in the estimation of manganese exposures

Age group (months)	Bodyweight (kg)
0 to <4	5.9[a]
4 to <6	7.8[b]
6 to <9	8.7[b]
9 to <12	9.6[b]
12 to <15	10.6[b]
15 to <18	11.2[b]
18 to <24	12.0[c]
24 to <60	16.1[c]

[a] DH, 1994
[b] DH, 2013
[c] Bates *et al*., 2014

Exposure from Breast milk

25. No consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months. Therefore, the default consumption values used by the COT in other evaluations of the infant diet of 800 and 1200 mL for average and high-level consumption have been used to estimate exposures to manganese from breastmilk. The ranges of mean and high-level exposure to manganese in exclusively breast-fed 0 to 6-month-old infants were 4.1 – 5.4 µg/kg bw/day and 6.1 – 8.1 µg/kg bw/day respectively (Table 3).

26. Data on breast milk consumption for infants and young children aged 4 to 18 months were available from the DNSIYC and the NDNS, and have been used to estimate exposures at these ages (Table 3), based on a mean manganese concentration of 40 µg/kg the highest breastmilk in the range reported by EFSA, 2013 (paragraph 12). There were too few records of breast milk consumption for children older than 18 months in the NDNS to allow a reliable exposure assessment, and breast milk is expected to contribute minimally in this age group.

27. Mean exposures to manganese for 4 to 18 month olds were 1.0 to 3.7 µg/kg bw/day, and 97.5th percentile exposures were 2.1 to 6.4 µg/kg bw/day (Table 3).

Table 3. Estimated Manganese exposure in 0 to 18-month-old infants and young children from breast milk, containing manganese at 40 µg/kg

Exposure (µg/kg bw/day)	Age group (months)					
	0 to <4	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18
Average	5.4[a]	4.1[a] 3.7[b]	2.7[b]	1.5[b]	1.2[b]	1.0[b]
High-level	8.1[a]	6.1[a] 6.2[b]	6.4[b]	4.6[b]	3.0[b]	2.1[b]

[a] Based on default consumption values of 800 and 1200 mL for average and high level exclusive consumption of breast milk.
[b] Based on mean and 97.5th percentile consumption of breast milk from DNSIYC (DH,2013)
Values rounded to 2 SF

Exposure from Infant formulae and complementary foods

28. Manganese exposure estimates for infant formulae and complementary foods were derived using occurrence data from the Infant Metals Survey (FSA, 2016a). The basis for this survey is explained in Annex A, but in brief, the exposure data derived from the Infant Metals Survey allow estimation of manganese exposure from infant formula, commercial infant foods and the most commonly consumed adult foods ('other foods') as sold.

29. Exposure estimates for 0 to 6 month olds were calculated for infants exclusively fed on 'first-milk' formulae using the default consumption values of 800 and 1200 mL (Table 4). In 0 to 6 month olds, exposures to manganese from exclusive feeding on ready-to-feed formula were 6.5 to 8.5 µg/kg bw/day in average consumers, and 10 to 13 µg/kg bw/day in high level consumers. Exposures to manganese calculated for reconstituted formula incorporating a manganese concentration in tap water taken from the 2014 TDS (2 µg/L) or the highest median (1.4 µg/L, from Table 1) and 97.5th percentile (15 µg/L from Table 1) were 9 to 14 µg/kg bw/day in average consumers, and of 14 to 21 µg/kg bw/day in high level consumers (Table 4).

Table 4. Estimated average and high-level exposures to manganese from exclusive feeding on infant formulae for 0 to 6 month olds

Infant Formula (concentration)	Manganese Exposure (µg/kg bw/day)			
	0 to <4		4 to <6	
	Average consumer (800 mL/day)	High level consumer (1200 mL/day)	Average consumer (800 mL/day)	High level consumer (1200 mL/day)
Ready-to-Feed[a]	8.5	13	6.5	10
Dry Powder[b,c]	12	18	9	14
Dry Powder[b]+ water at 2 µg/Lfrom TDS [d]	12	18	9	14

Dry Powder[b]+ water at 1.4 µg/L (highest median)[d]	12	18	9	14
Dry Powder[b]+ water at 15 µg/L (highest 97.5th percentile)[d]	14	21	10	16

[a] Exposure based on first milk infant formula using a manganese concentration of 63 µg/L
[b] Exposure based on first milk infant formula using a manganese concentration of 593 µg/kg
[c] Exposure does not include the contribution from water.
[d] Determined by applying a factor of 0.85 to default formula consumption of 800mL and 1,200mL per day for estimating water consumption.
Values rounded to 2 SF.

30. Consumption data from the DNSIYC were used to estimate exposures from infant formula and complementary foods for 4- to 18-month-olds (DH, 2013), based on upper-bound (UB) and lower-bound (LB) manganese concentrations in groups of complementary foods and levels detected in infant formula. Total mean exposures (excluding water) to manganese from infant formulae, commercial infant foods, and other foods, for 4 to 18-month-olds were 37 to 96 µg/kg bw/day, and 97.5th percentile exposures were 120 to 200 µg/kg bw/day (Table 4). These values are within the range of total intake of manganese that was reported in the DNSIYC survey for 4 to 18-month-old children (DH 2013). The presence of manganese in tap water at a level of 2 µg/L (TDS) or 15 µg/L (the highest 97.5th percentile value, derived from Table 1) made a negligible contribution to total exposure.

Table 5. Estimated exposures to manganese from infant formulae, commercial infant foods and other foods for 4 to 18 month olds

Values rounded to 2 SF

Manganese Exposure (LB-UB Range) (µg/kg bw/day)										
Food	**4 to <6 Months (n=116)**		**6 to <9 Months (n=606)**		**9 to <12 Months (n=686)**		**12 to <15 Months (n=670)**		**15 to <18 Months (n=605)**	
	Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
Infant formula	4.2-4.5	8.8-8.9	3.6-3.8	7.8-8.2	2.8-2.9	6.5-6.6	1.0-1.1	4.6	0.57-0.60	3.4-3.5
Commercial infant foods	19	81	27	85	24	91	14	65	8.2	42
Other foods	12	59	38	130	60	150	76	170	87	170
Total (excl. tap water)	37	120[a]	70	160[a]	88	200[a]	92	190	96	190[a]

[a] Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

[b].Manganese concentration for tap water was from 2014 TDS.

Exposure estimates based on foods in the TDS

31. Results from the TDS are based on analysis of food that is prepared as for consumption (FSA, 2016b). The consumption data from the DNSIYC were used for the estimation of exposure for children aged 12 to 18 months (DH, 2013) whereas consumption data from NDNS (Bates et al., 2014) were used for estimating exposure in older children. Exposure estimates based on data from the 2014 TDS are presented only as UB, because the few food groups with concentrations below the LOQ or the LOD (green vegetables, fresh fruit and nuts) had a minimal impact on the total dietary exposure. A more detailed breakdown of individual food groups for the TDS can be found in Annex B. Mean and 97.5th percentile exposures to manganese from a combination of all food groups of up to 140 and 290 µg/kg bw/day, respectively were derived (Table 5). These estimates of dietary exposure are comparable to the intake values for manganese which were reported in NDNS (Bates *et al* 2014) for 1.5 to 3 year old children. The presence of manganese in tap water at a level of 2 µg/L (TDS) or 15 µg/L (the highest 97.5th percentile value derived from Table 1) made a negligible contribution to total exposure. The food groups making the highest contribution to manganese exposure in the TDS were cereals and non-alcoholic beverages (Annexes A and B).

Table 6. TDS estimated dietary exposure to manganese in children aged 18 months to 5 years.

Manganese exposure (µg/kg bw/day)							
12 to <15 Months (n=670)		**15 to <18 Months (n=605)**		**18 to <24 Months (n=70)**		**24 to <60 Months (n=429)**	
Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
120	280	140	290	170	280	150	270

Values rounded to 2 SF

Soil and Dust

32. Exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to manganese in soil and dust were calculated assuming ingestion of 60 or 100 mg/day, respectively (US EPA, 2011a). Younger infants, who are less able to move around and come into contact with soil and dust, are likely to consume less soil than children of these age groups. Median and 90th percentile soil concentrations of 90 and 225 mg/kg respectively were used in these exposure estimations (paragraph 20) (Table 7). Since there were no specific data for levels in dust, the exposure calculations below were based on concentrations in soil, with the assumption that the value is the same as for dust.

33. The exposures in infants and young children based on the median and 90th percentile concentration of manganese range from 0.56 to 0.85 µg/kg bw/day and from 1.4 to 2.1 µg/kg bw/day respectively. These exposures are negligible in comparison to overall exposures from dietary sources.

Table 7. Potential manganese exposures (µg/kg bw/day) from soil and dust in infants and young children aged 6 to 60 months

Manganese concentration	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
Median (90 mg/kg)	0.62	0.56	0.85	0.80	0.75	0.56
90th percentile (225 mg/kg)	1.6	1.4	2.1	2.0	1.9	1.4

Values rounded to 2 SF.

Air

67. Potential exposures of UK infants aged 0 to 12 months and young children aged 1 to 5 years to manganese in air were estimated using the body weights shown in Table 2, and by assuming the mean ventilation rates presented in Table 8; these rates have been derived from the US EPA exposure factors handbook (US EPA, 2011b). The resulting exposures are presented in Table 9.

Table 8. Mean ventilation rates used in the estimation of manganese exposures from air (derived from US EPA, 2011b)

Age group (months)	Ventilation rate (m^3/day)
0 to <4	3.5
4 to <6	4.1
6 to <9	5.4
9 to <12	5.4
12 to <15	8.0
15 to <18	8.0
18 to <24	8.0
24 to <60	10.1

68. The manganese concentrations used in the exposure calculations were the lowest and highest median values and lowest and highest 99th percentile values of 0.73, 85, 1.6 and 155 ng/m3, respectively, from monitoring sites in the UK (see paragraph 22). Exposure to manganese from air is negligible compared to dietary exposures.

Table 9. Possible exposures to manganese in infants and young children from air

Manganese	Exposure (µg/kg bw/day)
	Ages (months)

concentration (ng/m^3)	0 to <4	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
0.73 (lowest median value)	0.00043	0.00038	0.00045	0.00041	0.00055	0.00052	0.00049	0.00046
85 (highest median)	0.050	0.044	0.053	0.048	0.064	0.061	0.057	0.053
1.6 (lowest 99th percentile value)	0.00094	0.0008	0.00099	0.0009	0.0012	0.0011	0.0011	0.0010
155 (highest 99th percentile value)	0.092	0.081	0.096	0.087	0.11	0.11	0.10	0.097

ADME and new data from animal studies

34. Manganese is present in a wide range of foods including cereals, vegetables, fruit, nuts, spices, wine, tea and coffee. This broad range is one of the reasons why deficiency is not observed in the general population (Roth, 2006). According to a number of sources, only 5% of dietary manganese is actually absorbed by the GI tract (Roth, 2006; [5.9 +/- 4.8%; range 0.8-16%Davidsson et al, 1989]; [Mean absorption: lettuce 5.2%, spinach 3.81%, sunflower seeds 1.71%, wheat 2.16%, $MnCl_2$ 8.9% Johnson et al, 1991]).

35. Once manganese has entered in to the circulation, it accumulates primarily in the liver (1.2-1.3 mg/kg), brain (0.15-0.46 mg/kg) and bone (from 1mg/kg upwards depending on exposure with up to 40% of the total body burden of manganese being found at autopsy). Manganese is detected in the cerebrospinal fluid before it is detected in the brain (O'Neal & Zheng, 2015).

36. Manganese is primarily excreted via the faeces through the hepatobiliary route. Small amounts are excreted via the urine and much lower amounts through breastmilk and sweat.

Human studies and case studies with excess manganese

37. A good quality systematic review and meta-analysis looking at the association between manganese, arsenic and cadmium exposure with neurodevelopment in children up to 16 years old, identified 41 relevant articles published between January 2000 and March 2012. Seventeen of these studies from a range of countries investigated manganese, including North and South America, Europe and Asia. Most studies looked at children aged between 5 and 15 years, but one French study looked at neonates and one from Mexico looked at children aged between 12 and 24 months. Manganese exposure was primarily assessed by blood levels, but some studies used multiple methods including concentration of manganese in hair and tooth samples, concentration in water and one looked at placental manganese concentration. Study designs were primarily cross-sectional (13 studies) but there

were also two case-control, 1 cohort and 1 prospective study. In summary, all studies found a positive association between manganese exposure and behavioural disorders in children aged between 5 and 15 years. The meta-analysis found that a 50% increase in manganese levels in hair would be associated with a decrease of 0.7 points ($p < 0.001$) in the Full-Scale IQ of children aged 6-13 years (Rodrigues-Barranco et al, 2013).

38. A literature search has been carried out of studies published since this review and those studies are summarised below. The search terms can be found in appendix 1.

39. A review looking at studies of manganese exposure in infants and young children (but without a meta-analysis) concluded that higher hair concentrations of manganese were consistently associated with lower I.Q. scores. Blood biomarkers compared to I.Q scores produced inconsistent results. The authors concluded that analysis of hair manganese was the most accurate method of determining manganese exposure in school-aged children and that no accurate methods are available for determination of manganese exposure in infants and toddlers, the population group considered most vulnerable to excess manganese (Coetzee et al, 2016).

40. A further review looking at cadmium, manganese and metal mixture exposure in early life and effects on cognition and behaviour concludes that evidence consistently shows that early life exposure to manganese has a negative impact on both cognition and behaviour with particularly consistent effects on IQ observed and some associations between early life exposure to elevated manganese and ADHD and autism (Sanders et al, 2015).

41. A review of the literature up to March 2016 for studies using a biomarker-based or environmental measurement of manganese exposure, and measurement of at least one neurological outcome for children aged 0-18 years identified 36 relevant papers. Study designs were cross-sectional (24), prospective cohorts (9), and case control (3). Neurodevelopmental outcomes were first assessed for Mn exposure in infants (6 papers), toddlers or preschoolers (3 papers) and school-age children (27 papers). IQ was the primary parameter measured in school-aged children and hair or blood manganese biomarkers were used. Higher hair manganese was consistently associated with lower IQ scores while studies of blood biomarkers and IQ scores had inconsistent findings. Studies of infants and toddlers most frequently measured mental and psychomotor development with inconsistent findings across biomarkers of manganese exposure. The authors conclude that research to identify biomarkers feasible for fetuses and infants is urgently needed given their unique vulnerability to excessive Manganese (Coetzee et al, 2016).

42. Children with Autism Spectrum disorder were found to have significantly elevated serum manganese levels compared to controls (+20%) (Skalny et al, 2017).

43. The brain is the primary organ of manganese toxicity. MRI scans of occupationally exposed individuals have shown manganese to accumulate preferentially in the globus pallidus area of the basal ganglia, partly responsible for the regulation of voluntary movement (O'Neal and Zheng, 2015).

44. MRI imaging of the brain structures of 10 children aged 9-15 years exposed to drinking water containing high manganese levels and 13 age matched controls (water concentrations not stated) revealed slightly enlarged brain structures in the high-manganese exposed group including the putamen, globus pallidus and the caudate (but these were not statistically significant). Significant differences in surface based morphometry of the bilateral putamen and similar, but not statistically significant trends were observed in the bilateral caudate and globus pallidus. Several sub-regions show significant enlargement in those individuals with higher manganese exposures, notably the left anterior globus pallidus. Assessment of motor performance in both groups showed a correlation between degree of enlargement and motor performance (Lao et al, 2017).

45. Deciduous teeth from 142 participants aged 11-14 years were used to measure the prenatal and postnatal manganese exposure in an area of Italy adjacent to a ferro-manganese plant. The Virtual Radial Arm Maze was used to assess visuospatial learning and memory. A U-shaped curve was produced in females for prenatal exposure in results for time taken to complete the task and the number of errors made. No effects were observed in males or for post-natal exposure to manganese (Bauer et al, 2017).

46. A similar study in Italy using deciduous teeth from 195 children aged 11-14 years in Italy was designed to assess motor function. Higher prenatal manganese exposure was associated with better body stability (mean sway, transversal sway, sagittal sway, sway area, and sway intensity) in boys but was inversely associated with these parameters in girls ($p < 0.05$). Higher prenatal manganese was also associated with better hand/finger co-ordination and hand/eye co-ordination in boys compared to girls but this did not reach statistical significance (Chiu et al, 2017).

47. Children diagnosed with ADHD in Malmo, Sweden (n=166) and age matched controls were identified and their umbilical cord blood (routinely taken and stored) was retrieved and analysed for manganese and selenium levels. In this study manganese in cord blood was not associated with a diagnosis of ADHD and this did not change after adjusting for confounders. Manganese/selenium ratio was also not associated with ADHD diagnosis ($p=0.81$) (Ode et al, 2015).

48. A Canadian pilot study in an area of Québec with high water manganese looked at 46 children aged 6-15 years of age. Two wells (W1and W2) were identified with water manganese levels of 610 and 160 µg/L respectively. Measures of hyperactivity (Revised Conners' Rating Scale for parents and teachers on sub-scales for Oppositional, Hyperactivity, Cognitive Problems/Inattention and ADHD) and hair manganese were recorded for each well. Children from W1 were found to have higher hair concentrations than W2 (mean 6.2 +/- 4.7 µg/g vs. 3.3 +/- 3.0 µg/g; $p = 0.025$). Elevated hair manganese was significantly associated with higher scores for oppositional ($p = 0.02$) and hyperactivity ($p = 0.002$) behaviours (Bouchard et al, 2007).

49. In a follow-up study in the same area with 362 children aged 6-13 years, levels of manganese in tap water and hair samples were measured, I.Q. assessed and dietary intakes of manganese were estimated using food frequency questionnaires. Median water manganese levels were 34 µg/L (1-2700 µg/L). Hair manganese levels correlated with water manganese levels but did not correlate with

estimated dietary intake. Elevated water manganese and hair manganese levels were significantly associated with lower I.Q. scores with a 10-fold increase in exposure from water equating to a decrease in 2.4 I.Q points after adjusting for confounders (95% confidence interval, -3.9 to -0.9, p = <0.01) (Bouchard et al, 2011).

50. The same group replicated this study in the New Brunswick area of Canada where manganese levels in well-water are relatively high. Children aged 6-13 years (n=259) were recruited and domestic tap water (from well sources only), hair, toe nail and saliva samples were taken for each child. Each child completed 4 sub-tests of the Wechsler Intelligence scale for Children (4^{th} edition). In girls, higher manganese concentration in water, hair, and toe nail were associated with poorer Performance IQ scores but this was significant only for toe nail (for a 10-fold increase in manganese, β - 5.65, 95% CIs: 10.97, 0.32). Opposite associations were observed in boys: better Performance IQ scores with higher manganese concentration hair, toe nail, and water, the latter being significant (β: 2.66, 95% CIs: 0.44, 4.89). Verbal IQ scores did not seem to be associated with manganese exposure indicators Bouchard et al, 2017).

51. A further follow-up study in the same cohort, asked participants to complete a battery of tests designed to assess neuro-behavioural functions including memory, attention, motor function and hyperactivity. Following adjustment for confounders, a 1 standard deviation increase in Log_{10} hair manganese was associated with a significant reduction in scores for memory and attention (–24% (95% CI: –36, –12%) SD for memory and –25% (95% CI: –41, –9%) SD for attention) (Oulhote et al, 2014).

52. The same cohort was followed up 4 years after the 2011 study above, and 287 children participated in a follow-up study looking at manganese in drinking water and IQ at adolescence. Tap water and hair manganese samples were analysed again and compared to I.Q scores. Mean water manganese concentration at follow-up was 14.5mg/L. Higher water manganese at follow-up was associated with lower I.Q. in girls (β for a 10-fold increase = -2.8, 95% confidence intervals -4.8 to -0.8) and higher I.Q. in boys (β = 3.9, 95% CI 1.4 to 6.4). IQ scores were not significantly associated with hair manganese concentrations, although similar trends as for water were observed (Dion et al, 2017).

53. Maternal and cord blood samples taken from 224 mother-infant pairs from an area of Oklahoma USA known for its industrial activity and a site of mine waste pollution, rich in metals. Blood samples were analysed for manganese. At two years of age, the neurodevelopment of the children was assessed using the Bayley Scale of infant development. Median (25^{th} – 75^{th} percentile) maternal and cord blood concentrations were 24.0 µg/L (19.5 – 29.7 µg/L) and 43.1 µg/L (33.5 - 52.1 µg/L) respectively. After adjusting for lead, arsenic and other confounders, an interquartile range increase on maternal blood manganese (10.1 µg/L) was associated with 3 point decrement in mental development indices (95% CI; -5.3; -0.7) and a 2.3 point decrement in psychomotor development indices (95% CI; -4.1, -0.4). Cord blood was not associated with mental and psychomotor development indices. The authors conclude that more work is needed in this area (Claus-Henn et al, 2017).

54. In Ohio, USA, 404 children aged 7-9 were enrolled and blood and hair samples were taken and analysed for manganese and lead concentration and serum was analysed for cotinine. IQ scores were assessed for each child. Geometric mean blood (n = 327) and hair manganese (n = 370) concentrations were 9.67 ± 1.27 µg/L and 416.51 ± 2.44 ng/g, respectively. After adjusting for potential confounders, both low and high blood and hair manganese concentrations were associated with lower Full Scale IQ and subscale scores, with significant negative associations between the highest quartile and middle two quartiles of blood manganese (β –3.51; 95% CI: –6.64, –0.38) and hair manganese (β –3.66; 95% CI: –6.9, –0.43%) and Full Scale IQ (Haynes et al, 2015).

55. Manganese in deciduous teeth was used to identify prenatal and postnatal exposure to manganese in 193 Californian children and this was compared to neurodevelopment measured using the Mental Development Index (MDI) and Psychomotor Development Index (PDI) on the Bayley Scales of Infant Development at 6, 12, and 24-months. A two-fold increase in postnatal manganese exposure was associated with 0.8-point decrease (95% CI: 1.4, 0.2) in MDI at 6-months and 0.9-point decrease at 12-months of age (95% CI: 1.8, 0.1). A non-linear relationship between postnatal manganese exposure and PDI at 6-months was observed. A significant interaction between postnatal manganese exposure and sex was observed for both MDI (p=0.02) and PDI (p=0.03) at 6-month. There was a significant inverse relationship between postnatal manganese exposure and neurodevelopment at 6-months with stronger effects among girls for both MDI (-1.5 points; 95% Confidence Interval (CI): -2.4, -0.6) and PDI (-1.8 points; 95% CI: -3.3, -0.3). No relationship was observed amongst boys. Girls whose mothers had lower haemoglobin levels experienced larger decreases in MDI and PDI associated with prenatal manganese levels than girls whose mothers had higher haemoglobin levels (p = 0.007 and 0.09, respectively). No interactions were observed with blood lead concentrations or any relationships with neurodevelopment at 24-months (Gunier et al, 2015)

56. Children aged 7-9 years living close to a ferro-manganese plant in Ohio USA (n=55) participated in a postural balance assessment and hair and blood samples were taken and analysed for manganese and lead. Hair and blood manganese and distance from the plant were all significantly associated with poor postural balance. In addition, low-level blood lead was negatively associated with balance outcomes. The authors conclude that manganese exposure and low-level blood lead are significantly associated with poor postural balance (Rugless et al, 2014).

57. In a large cohort of 17000 children from North Carolina, USA, 1.7% were found to have speech or language disorders, 0.24% were found to have delayed milestones and 0.026% were diagnosed with hearing loss. Manganese, arsenic and lead concentrations were measured in representative well water samples and these were compared to the location of the children with hearing loss, delayed milestones or speech and language disorders. The mean county concentration of manganese in private wells was significantly and positively associated with the prevalence of delayed milestones (log relative risk 0.39; 95% confidence interval: 0.18, 0.61). This is equivalent to a 48% increase in the risk of delayed milestones [exp(0.39)=1.48] corresponding to a one standard deviation unit increase in the county's average private well manganese concentration. The mean county arsenic and lead

concentrations were not associated with the prevalence of delayed milestones. An increase in the mean county manganese well water concentration was associated with an increase in the prevalence of hearing loss (log relative risk 0.14, 95% confidence interval: 0.03, 0.026). This is equivalent to a 15% increase in the risk of hearing loss (exp(0.14)=1.15) corresponding to a one standard deviation unit increase in the county's average private well manganese concentration (Langley et al, 2015).

58. Carers of Jamaican children with Autistic Spectrum Disorders (ASD) (n=109) and age matched controls aged 2-8 years were administered a questionnaire to assess demographic and socioeconomic information, medical history, and potential exposure to manganese. Blood samples from each child were analysed for manganese levels. General Linear Models (GLM) were used to test the association between blood manganese and ASD. In univariable GLM no significant association between blood manganese and ASD was observed (10.9 µg/L for cases vs. 10.5 µg/L for controls; p = 0.29). In a multivariable GLM adjusting for paternal age, parental education, place of child's birth, consumption of root vegetables, cabbage, saltwater fish, and cakes/buns, there was still no significant association between blood manganese and ASD status, (11.5 µg/L for cases vs. 11.9 µg/L for controls; p = 0.48) (Rahbar et al, 2014).

59. A study in Brazil, looking at 83 children living near a ferro-manganese plant and their caregivers, assessed hair and blood manganese levels, blood lead levels and cognitive performance was assessed using the Wechsler Intelligence Scale for Children and Raven's Standard Progressive Matrices were used for the caregivers. Children's mean hair and blood manganese levels were 5.83 µg/g (0.1 – 86.68 µg/g) and 8.2 µg/L (2.7 – 23.5 µg/L) respectively. Mean maternal hair manganese was 3.50 mg/g (0.10–77.45) and correlated to children's hair manganese levels. Child and care-givers cognitive performance scores were negatively associated with elevated hair manganese. No such correlations were observed for blood manganese (Menezes-Filho et al, 2011)

60. A follow-up to this study found hair manganese to correlate significantly with distance from the plant. Mean hair manganese from exposed (<1.8km from the plant) and non-exposed (~7.5 km from the plant upwind) were measured as 15.2 µg/g (1.1 - 95.5 µg/g) for the exposed children and 1.37 µg/g (0.39-5.58 µg/g) for the non-exposed children (Menezes-Filho et al, 2016).

61. In Southern Brazil, 63 children aged 6–12 years, with 43 from a rural area and 20 from an urban area were recruited. Manganese was quantified in blood, hair and drinking water using inductively coupled plasma mass spectrometry (ICP-MS). Neuropsychological functions assessed included attention, perception, working memory, phonological awareness and inhibition. Intelligence quotient (IQ) was also evaluated. The biomarkers malondialdehyde (MDA), protein carbonyls (PCO), δ-aminolevulinate dehydratase (ALA-D), reactivation indexes with dithiothreitol (ALA-RE/DTT) and ZnCl2 (ALA-RE/ZnCl2), non-protein thiol groups, as well as microalbuminuria (mALB) level and N-acetyl-β-D-glucosaminidase (NAG) activity were assessed. The results demonstrated that manganese levels in blood, hair and drinking water were higher in rural children than in urban children ($p<0.01$). Adjusted for potential confounding factors (IQ, age, gender and parents' education) significant associations were observed mainly between blood manganese and visual attention

(β = 0.649; p<0.001), visual perception and phonological awareness. Hair manganese was inversely associated with working memory, and water manganese was associated with a decreased performance in written language and inhibition. Oxidative damage to proteins and lipids, as well as alteration in kidney function biomarkers was observed in rural children (p<0.05). Significant associations were found between blood, hair and water manganese levels and biomarkers of oxidative damage and kidney function and between some oxidative stress biomarkers and neuropsychological tasks (p<0.05) (Nascimento et al, 2016).

62. Ninety-three children born or living in a mining region of Ecuador were selected. A neurobehavioral test battery consisting of 12 tests (Raven's Progressive Color Matrices Scale PCM) assessing various neurobehavioual functions was applied as well as a questionnaire regarding mothers exposure to contaminants during the perinatal period. Hair samples were taken from children to determine manganese concentrations. Having controlled for age and educational level, children with elevated levels of hair manganese (over 2 µg/g) had poor performance in neurobehavioral tests. Children with elevated levels of manganese in the river water (970 µg/L) are the ones who have the highest levels of hair manganese and the worst performance in neurobehavioral tests (Betancourt et al, 2015).

63. Hair samples from 60 children aged 14-45 months from Montevideo, Uruguay were analysed for manganese and lead. Children were assessed with the Bayley Scales of Infant Development III. Mean hair manganese and lead concentrations were 0.98 ± 0.74 and 10.1 ± 10.5 µg/g, respectively. Before adjusting for confounders, inverse associations were observed between manganese and BSID scores, with girls having lower scores relating to manganese than boys. After adjustment for confounders, no relationships were found between hair manganese and BSID scores except when stratified by sex, boys had a positive association between hair manganese and language scores (Rink et al, 2014).

64. A Mexican study designed to assess the effects of manganese on visuoperception and visual memory was carried out in 267 children aged between 7 and 11 years old in one mining region where environmental manganese levels are considered to be high and a control non-mining region. Hair manganese was used to assess manganese exposure. Mean hair manganese was found to be 9 times higher in the mining region compared to the control region. The Rey-Osterrieth complex figure test was used where a complex figure is copied then drawn again from memory. Hair manganese levels were significantly associated with an increase in distortion errors, angle errors and overtracing of lines in the copy phase and an increase in overtracing and omissions and negatively associated with the number of areas drawn correctly, total score and percentage of immediate recall in the recall phase (p = <0.01) (Hernández-Bonilla et al, 2016).

65. Another Mexican study measured manganese concentration in maternal blood taken in the third trimester of pregnancy and cord blood samples taken at birth from 541 mother-infant pairs. Child neurodevelopment was assessed at 24 months of age using the Bayley Scales of infant and toddler neurodevelopment by blinded psychologists. Mothers were assessed for depression during the third trimester of pregnancy. Mean cord blood and maternal blood manganese concentrations were 50.1 (SD 16.5) µg/L and 27.7 (SD 8.7) µg/L. An increase in maternal blood manganese and the presence of depression symptoms were significantly associated

with a decrease in cognitive scores, language scores and motor scores after adjustment for confounders. No effects were observed when mothers showing symptoms of depression and no symptoms were compared. The authors acknowledge that this would require a larger more rigorous study to show a significant association between manganese exposure, depression and child development (Muñoz-Rocha et al, 2017).

66. Blood samples were taken at birth from 448 children in Mexico City. Lead and manganese levels were measured in blood at 12 and 24 months and neurodevelopment was measured at 6 monthly intervals from 12 to 36 months using the Bayley Scales of Infant Development II. At 12 months of age, the mean (SD) blood manganese level was 24.3 (4.5) µg/L and the median was 23.7 µg/L; at 24 months, these values were 21.1 (6.2) µg/L and 20.3 µg/L, respectively. Twelve- and 24-month manganese concentrations were correlated (Spearman correlation = 0.55) and levels declined over time (β = -5.7 [95% CI = -6.2 to -5.1]). The authors observed an inverted U-shaped association between 12-month blood manganese and concurrent mental development scores (compared with the middle 3 manganese quintiles, for the lowest manganese quintile, [beta] = -3.3 [-6.0 to -0.7] and for the highest manganese quintile, β = -2.8 [-5.5 to -0.2]). This 12-month manganese effect was apparent but diminished with mental development scores at later ages. The 24-month manganese levels were not associated with neurodevelopment (Claus Henn et al, 2010).

67. In a follow-up to this study using results from 455 children, mean (SD) blood concentrations at 12 and 24 months were, respectively, 24.7 (5.9) µg/L and 21.5 (7.4) µg/L for manganese and 5.1 (2.6) µg/dL and 5.0 (2.9) µg/dL for lead. Lead toxicity appeared to be increased amongst children with the highest manganese exposures. A significant manganese–lead interaction was observed only at 18 months for children in the highest quintile of 12-month blood manganese [β = –1.74 (95% CI: –3.00, –0.49)]. At 18 months, Mental Development (MDI) scores are expected to decline 0.01 points per 1-µg/dL increase in lead among children with midrange manganese levels, compared with 1.80 points (i.e., –0.05 + –0.01 + –1.74) among children with high manganese levels. Although effect estimates at other time points of MDI were not statistically significant, coefficients were all negative and approached significance at 24 months of age (p = 0.07). A similar but less pronounced relationship was observed for psychomotor development (PDI) (Claus Henn et al, 2012).

68. Fifteen subjects aged 6-7 were selected from an ongoing longitudinal birth cohort study in Mexico City. These individuals were selected because they had a second or third trimester blood sample analysed for metals and a neurodevelopmental assessment completed at 5 years of age. Maternal blood manganese concentrations ranged from 2.7 – 41.1 µg/L. Families consented to functional magnetic resonance imaging (fMRI). Children exposed to higher maternal blood manganese in utero appeared to have reduced functional connectivity between the insula and the occipito-temporal regions of the brain and the right globus pallidus and the dorsal ACC regions of the brain. Additionally a quadratic relationship was observed between manganese exposure and functional connectivity between the right globus pallidus and the inferior frontal gyrus.

69. A study in Mexico recruited 79 7- to 11-year-old children living in the Molango manganese-mining district and 95 age-matched children from a non-exposed community in the same State. The Children's Auditory Verbal Learning Test (CAVLT) was administered. Blood and hair samples were obtained to determine manganese concentrations using atomic absorption spectrophotometry. CAVLT performance was compared between the two groups and multilevel regression models were constructed to estimate the association between biomarkers of manganese exposure and the CAVLT scores. The exposed group presented higher hair and blood Mn ($p<0.001$) than the non-exposed group (median 12.6 vs. 0.6 µg/g, 9.5 vs. 8.0 µg/L respectively), as well as lower scores ($p<0.001$) for all the CAVLT subscales. Hair manganese was inversely associated with most CAVLT subscales, mainly those evaluating long-term memory and learning (β=-0.47, 95% CI -0.84, -0.09). Blood manganese levels showed a negative but non-significant association with the CAVLT scores (Torres-Agustín et al, 2013).

70. In Bangladesh, the presence of arsenic in surface waters has necessitated the need for deeper wells which are higher in manganese. The cognitive abilities and behaviour of 1265 10-year old children were assessed using the Wechsler Intelligence scale for Children IV and a Strengths and Difficulties Questionnaire. Water manganese concentration from water used by the mothers during pregnancy and by the children at 5 and 10 years of age was analysed by ICPMS. The median water manganese concentration was 0.20 mg/L (range 0.001–6.6) during pregnancy and 0.34 mg/L (<0:001–8:7) at 10 y. Analysis of results from children with low arsenic exposure showed that manganese exposure was not associated with the children's cognitive abilities. The interaction between gender and water manganese concentration was significant for IQ, verbal comprehension, working memory and processing speed ($p < 0.1$). Stratifying by gender (p for interaction in general <0.081) showed that low prenatal water manganese (<3 mg=L) was positively associated with cognitive ability measures in girls but not in boys. Water manganese concentrations at all time points were associated with an increased risk of conduct problems, statistically significant in boys (range 24–43% per mg/L) but not girls. At the same time, the prenatal water manganese concentration was associated with a decreased risk of emotional problems [odds ratio (OR) =0.39 (95% CI: 0.19, 0.82)] in boys. In girls, water manganese concentration was mainly associated with low prosocial scores [prenatal W-Mn: OR=1.48 (95% CI: 1.06, 1.88)]. Manganese levels in water consumed at 5 and 10 years of age did not have a statistically significant effect on cognitive abilities and behaviour (Rahman et al, 2017).

71. Another study in 3 regions of Bangladesh designed primarily to identify the effects of blood lead on neurodevelopmental outcomes recruited mothers during the first trimester of pregnancy and followed their offspring (n=524) until 20 months of age. Water samples from the primary drinking source were taken at recruitment and at 1, 12 and 20-40 months of age and analysed for lead, arsenic and manganese. At 40 months of age, blood samples were taken and analysed for lead; and neurodevelopmental tests were carried out. Water manganese concentrations appeared to correlate with fine motor scores (β2Ln water Mn = −0.08, SE = 0.03, p = 0.02). The authors conclude that at low levels of manganese exposure in water (<400 µg/L) manganese is beneficial to fine motor development but at higher levels manganese can be detrimental (Rodrigues et al, 2016).

72. A Chinese cohort of 377 mothers was recruited during birth when samples of cord blood were taken and analysed for manganese and brain-derived neurotrophic factor (BDNF). At 12 months of age the children underwent neurodevelopmental assessment. After adjusting for confounding factors, serum manganese level was significantly associated with gross motor scores (β = -6.0, 95% CI: -11.8 to -0.2, $p < 0.05$) and personal/social scores (β = -4.2, 95% CI: -8.4 to 0.1 $p < 0.05$). BDNF level was positively correlated with personal/social score (β = 0.7, 95% CI: 0-1.4, $p < 0.05$). A significant correlation was found between manganese and BDNF ($r = - 0.13$, 95% CI: -0.23 to -0.03, $p < 0.01$). Furthermore, the interaction between cord serum manganese and BDNF was significant ($p < 0.001$). The authors conclude that elevated prenatal manganese exposure was associated with impaired neurodevelopment which may be mediated by BDNF (Yu et al, 2016).

73. Nine hundred and thirty three mother – new-born pairs from Shanghai, China were recruited to explore the relationship between cord blood manganese concentrations and the results of neonatal behavioural neurological assessments (NBNA). The NBNA has 5 sections to assess behaviour, active tone, passive tone, primary reflexes and general assessment. The median serum manganese concentration was 4.0 µg/L. After adjusting for potential confounders, a high level of manganese (>/=75th percentile) was associated with a lower NBNA score (adjusted ß= -1.1, 95% CI: -1.4–0.7, $p<0.01$) and a higher risk of low NBNA (adjusted OR=9.4, 95% CI: 3.4–25.7, $p<0.01$). A nonlinear relationship was observed between cord serum manganese and NBNA after adjusting for potential confounders. NBNA score decreased with increasing manganese levels after 5.0 µg/L(LgMn>/=0.7). The cord serum manganese >/=5.0 µg/L had adverse effects on behaviour, active tone and general reactions ($p<0.001$) (Yu et al, 2014).

74. A case-control study of neural tube defects was carried out in northern China incorporating 80 cases and 50 controls. Samples of placenta were analysed for manganese, iron, copper, zinc and selenium. The median manganese concentration was 131.60 ng/g in case placentas and 101.54 ng/g in control placentas ($p < 0.001$). The median concentrations of Cu and Zn were significantly higher in the case group than in the control group. The association between higher concentrations of manganese and risk of neural tube defects showed a clear dose–response relationship. The risk of NTDs increased to 1.51 (95% CI, 0.65–3.52) and 5.03 (95% CI, 1.89–13.33) in the second and third tertiles, respectively, compared with the lowest tertile (Liu et al, 2013).

75. From a cohort of South Korean mothers, a total of 265 mother and child pairs had maternal blood samples taken during pregnancy and neurodevelopmental testing (using the Bayley Scales of Infant Development II (BSID-II)) at 6 months of age. Participants completed questionnaires on demographics, socioeconomic parameters and 24-hour food recall. Follow-up visits were scheduled every 6 months until 3 years of age. Arithmetic mean maternal blood manganese concentration was 22.5 ± 6.5 µg/L and the median was 21.3 µg/L. At 6 months of age, the mean BSID-II scores were 94.4 ± 11.7 and 93.4 ± 14.3 for MDI and PDI, respectively. The author's observed no significant sex differences in BSID-II. Children from the group with maternal blood manganese of 25.0–29.9 µg/L demonstrated higher 6-month neurodevelopmental scores (MDI and PDI) compared with children in the highest

manganese group (≥ 30.0 µg/L) and the lowest manganese group (< 20 µg/L) (Chung et al, 2015).

76. Forty clinic referred children with ADHD and forty three controls aged 6-15 years were recruited from the Seoul region of South Korea. Each participant took an intelligence test and provided a hair sample for manganese analysis. After controlling for confounders including age and sex, higher hair manganese concentrations was significantly associated with ADHD (OR=6.40, 95% CI=1.39–29.41, p=0.017) (Shin et al, 2015).

77. In a North Korean cohort of 890 children, children were assessed for ADHD and emotional and behavioural problems and their IQ tested. Blood samples were taken and analysed for manganese. A significant interaction was identified between ADHD status and blood manganese concentration in predicting scores for anxiety/depression, social problems, delinquent and aggressive behaviour, internalising and externalising problems. No associations were found in children without ADHD (Hong et al, 2014).

78. Children aged 8-11 years (n=1089) were recruited from 5 representative regions of South Korea. Blood lead and manganese levels and urinary cotinine levels were determined and children underwent a battery of tests designed to assess IQ, attention, academic functions, emotional and behavioural problems. Median blood Manganese was 14.14 µg/L. After adjusting for urine cotinine, blood lead, children's IQ, and other potential confounders, the high manganese group showed lower scores in thinking (B=−0.83, p=0.006), reading (B=−0.93, p=0.004), calculations (B=−0.72, p=0.005), and learning quotient (B=−4.06, p=0.006) and a higher commission error in the continuous performance test (B=8.02, p=0.048). The low manganese group showed lower colour scores in the Stroop test (B=−3.24, p=0.040) (Bhang et al, 2014).

79. Cord blood samples were taken from 230 mothers from Taiwan who were recruited at parturition. Blood samples were then analysed for manganese, lead, arsenic and mercury and the children were assessed for neurodevelopment at 2 years of age using the Comprehensive Developmental Inventory for infants and toddlers (CDIIT). Median cord blood concentrations of manganese, lead, arsenic and mercury were 47.90 mg/L (range, 17.88–106.85 mg/L), 11.41 mg/L (range 0.16–43.22 mg/L), 4.05 mg/L (range, 1.50–12.88 mg/L) and 12.17 mg/L (range, 1.53–64.87 mg/L), respectively. After adjusting for confounders, manganese and lead levels above the 75th percentile were found to have a significant adverse association with the overall (β=−7.03, SE=2.65, p0.0085), cognitive (β=−8.19, SE=3.17, p=0.0105), and language quotients (β=−6.81, SE=2.73, p=0.0133) of the CDIIT (Lin et al, 2013).

Risk characterisation

80. There appears to be a significant amount of literature indicating a link between elevated manganese exposure and neurodevelopmental effects in children. Most of these studies have measured manganese exposure through hair, blood or tooth analysis and very little has been done to relate this to dietary exposures. The one study that did attempt to estimate dietary manganese did not show a relationship between hair manganese levels and estimated dietary exposure. Many of these

studies are confounded by exposure to other substances that may affect neurodevelopment such as lead (Bouchard et al, 2011).

81. Many of the available studies primarily focus on industrial areas where environmental manganese is high or areas where drinking water naturally contains high levels of manganese. But there are also a number of studies where this does not appear to be the case.

82. The WHO derived a TDI of 60 µg/kg body weight/day in the Guidelines for Drinking Water Quality (WHO, 2011). This was based on the upper range intake of 11mg/day derived from survey data of Western diets carried out by the US-based Institute of Medicine (IOM). The WHO concluded that this amount did not represent an over-exposure to manganese. Additionally, the WHO considered a study by David & Greger (1992) where women supplemented with 15mg/day of manganese chelated with amino acids for 90 days showed no adverse effects other than a significant increase in lymphocyte manganese-dependent superoxide dismutase, a known biomarker that increases with increasing manganese exposure. The new data described in this statement do not provide adequate information to update this HBGV and therefore the WHO TDI has been compared against exposures calculated for UK infants and children. Table 10 below compares exposures at different age ranges and shows that a number of groups exceed the WHO TDI for manganese. Mean and 97.5th percentile children aged 6 to 60 months and 97.5th percentile infants aged 4-6 months receiving weaning foods all appear to exceed the TDI set by the WHO.

83. It appears that absorption of manganese in the gastro-intestinal tract is low so it is unclear if these intakes would be considered of concern.

Table 10: Exposures for manganese in children up to 5 years old (µg/kg body weight/day)

Age		0-<4 months	4-<6 months	6-<9 months	9-<12 months	12-<15 months	15-<18 months	18-<24 months	24-<60 months
Health-based guidance values	WHO	TDI of 60 µg/kg bw/day							
Mean bodyweight for age group (a)		5.9	7.8	8.7	9.6	10.6	11.2	12.0	16.1
Mean exposures (µg/kg bw/day)	Breastfed	5.4(b)	4.1(b)	70(d)	88(d)	92-120(e)	96-140(e)	170(f)	150(f)
	Exclusively formula fed	14(c)	10(c)						
	Weaning diet and formula	-	37(d)						
97.5th percentile exposures (µg/kg bw/day)	Breastfed	8.1(b)	6.2(b)	160(d)	200(d)	190-280(e)	190-290(e)	280(f)	270(f)
	Exclusively formula fed	21(c)	16(c)						
	Weaning diet and formula	-	120(d)						

Exposure to soil and dust has not been included in this table as their contribution to total exposure is minimal.
Ranges are based on upper bound and lower bound figures for manganese concentration in foods.

a) Taken from Table 2 in this document.
b) Taken from Table 3 in this document.
c) Taken from Table 4 in this document.
d) Taken from Table 5 in this document.
e) Taken from Tables 5 & 6 in this document.
f) Taken from Table 6 in this document.

COT Conclusions:

84. The Committee concluded that there was evidence that associated excessive exposure to manganese with adverse effects on neurodevelopment in young children. This has primarily been associated with exposure as a result of industrial processes occurring in the vicinity of children's homes or a parent working in such an environment but this may be confounded by the presence of other contaminants.

85. Members stated that whilst the proliferation of data on the effects of high exposures to manganese on the neurodevelopment of young children was useful, it was difficult to relate these to dietary exposures. Limitations include possible confounding by lead and other neurodevelopmental toxins, applicability of the biomarkers used and lack of data on the proportion of manganese absorbed in the dietary tract. Members noted that there is a lack of evidence to suggest that current dietary exposures cause adverse neurodevelopmental effects. More evidence is necessary to draw conclusions on current intakes of manganese.

86. Members noted the use of several different biomarkers used to determine manganese exposure in the recently published literature, including blood, hair and deciduous teeth. They agreed that of the biomarkers used, blood manganese is likely to be the most useful. However, manganese may be actively taken up into the red blood cells and therefore this may have its limitations as an accurate marker of manganese exposure.

87. A number of studies showed differences in effects observed in male and female children with similar exposures. Higher manganese exposure was associated with positive effects in males and negative effects in females. The Committee were not able to comment on the reasons for this, but with other neurodevelopmental toxins, differences in blood flow in the brain between males and females was thought to have an effect.

88. The COT discussed the use of the WHO TDI, derived as part of the Drinking Water Quality Guidelines. Members considered this TDI to be relatively conservative as it is derived from a manganese intake from dietary surveys that is considered to cause no adverse effects with an additional safety factor of 3 to take account of increased bioavailability from water.

89. Members concluded that it was not possible to relate the adverse effects observed in humans to dietary exposures and therefore it is not possible to draw firm conclusions on the effects of current dietary exposures on the neurodevelopment of children ages 0-5 years. Further data is required to refine this risk assessment.

Committee on Toxicity
xxxx 2018

References

Ander EL, Watts MJ, Smedley PL, Hamilton EM, Close R, Crabbe H, Fletcher T, Rimell A, Studden M and Leonardi G (2016) Variability in the chemistry of private drinking water supplies and the impact of domestic treatment systems on water quality. Environ. Geochem. Health. 38, 1313-1332

Bauer JA, Henn BC, Austin C, Zoni S, Fedrighi C, Cagna G, Placidi D, White FR, Yang Q, Coull BA, Smith D, Lucchini RG, Wright RO, Arora M. (2017) Manganese in teeth and neurobehavior: Sex-specific windows of susceptibility.

Betancourt Ó, Tapia M, Méndez I. (2015) Decline of General Intelligence in Children Exposed to Manganese from Mining Contamination in Puyango River Basin, Southern Ecuador. Ecohealth. Sep;12(3):453-60

Bhang SY, Cho SC, Kim JW, Hong YC, Shin MS, Yoo HJ, Cho IH, Kim Y, Kim BN (2013) Relationship between blood manganese levels and children's attention, cognition, behavior, and academic performance--a nationwide cross-sectional study. Environ Res. Oct;126:9-16.

Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D (2007) Hair Manganese and Hyperactive Behaviours: Pilot Study of School-Age Children Exposed through Tap Water. Environ Health Perspect. 115 (1) 122-127

Bouchard MF, Sauvé S, Barbeau B, Legrand M, Brodeur M-E, Bouffard T, Limoges E, Bellinger DC, Mergler D (2011) Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water. Environ Health Perspect 119:138-143

Bouchard MF, Surette C, Cormier P, Foucher D (2017) Low level exposure to manganese from drinking water and cognition in school-age children. Neurotoxicology Jul 15. pii: S0161-813X(17)30154-7

British Geological Survey (BGS) (2012): Rawlins, B G, McGrath, S P, Scheib, A J, Breward, N, Cave, M, Lister, T R, Ingham, M, Gowing, C and Carter, S. (2012). The advanced soil geochemical atlas of England and Wales. British Geological Survey, Keyworth. www.bgs.ac.uk/gbase/advsoilatlasEW.html

British Nutrition Foundation: National Diet and Nutrition Survey rolling programme - year 1 and 2 (combined) results. 2011. http://www.nutrition.org.uk/nutritioninthenews/new-reports/ndns-year-2 (accessed January 4, 2013).

Cao S, Duan X, Zhao X, Chen Y, Wang B, Sun C, Zheng B, Wei F. (2016) Health risks of children's cumulative and aggregative exposure to metals and metalloids in a typical urban environment in China. Chemosphere 147, 404-411

Chiu Y-H M, Claus Henn B, Leon Hsu H-H, Pendo MP, Coulle BA, Austin C, Cagna G, Fedrighi C, Placidi D, Smith DR, Wright RO, Lucchini RG , Arora M (2017) Sex differences in sensitivity to prenatal and early childhood manganese exposure on

neuromotor function in adolescents. Environmental Research Volume 159, November 2017, Pages 458-465

Chung SE, Cheong HK, Ha EH, Kim BN, Ha M, Kim Y, Hong YC, Park H, Oh SY (2015) Maternal Blood Manganese and Early Neurodevelopment: The Mothers and Children's Environmental Health (MOCEH) Study. Environ Health Perspect. 2015 Jul;123(7):717-22

Claus Henn B, Bellinger DC, Hopkins MR, Coull BA, Ettinger AS, Jim R, Hatley E, Christiani DC and Wright RO (2017) Maternal and Cord Blood Manganese Concentrations and Early Childhood Neurodevelopment among Residents near a Mining-Impacted Superfund Site. Environ Health Perspect. Jun 28;125(6)

Claus Henn B, Schnaas L, Ettinger AS, Schwartz J, Lamadrid-Figueroa H, Hernández-Avila M, Amarasiriwardena C, Hu H, Bellinger DC, Wright RO, Téllez-Rojo MM (2012) Associations of Early Childhood Manganese and Lead Coexposure with Neurodevelopment Environ Health Perspect 120:126-131

Claus Henn B, Ettinger AS, Schwartz J, Téllez-Rojo MM, Lamadrid-Figueroa H, Hernández-Avila M, Schnaas L, Amarasiriwardena C, Bellinger DC, Hu H, Wright RO. (2010) Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology. Jul;21(4):433-9.

Coetzee DJ, McGovern PM, Rao R, Harnack LJ, Georgieff MK, Stepanov I (2016) Measuring the impact of manganese exposure on children's neurodevelopment: advances and research gaps in biomarker-based approaches. Environ Health. Aug 30; 15(1):91

Department of Health. Dietary reference values for food, energy and nutrients in the United Kingdom No. 41. London: HMSO, 1991.

DH (Department of Health), (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

DWI (2008) Review of England and Wales Monitoring Data for Which a National or International Standard Has Been Set. Available at: http://www.dwi.gov.uk/research/completed-research/reports/DWI70_2_215_Monitoring_Data.pdf (accessed xxxxx)

EFSA (2006) Tolerable Upper Intake Levels for Vitamins and Minerals. Available at: http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf

EU (2016) Commission delegated regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding. Available at : http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0127&from=EN (Accessed 13/09/16)

FSA (2016a) Survey of metals and other elements in infant foods (to be published).

FSA (2016b) Metals and other elements in the 2014 Total Diet Study (to be published).

Fulk F, Succop P, Hilbert TJ, Beidler C, Brown D, Reponen T, Haynes EN. (2017) Pathways of inhalation exposure to manganese in children living near a ferromanganese refinery: A structural equation modeling approach. Science of The Total Environment 579 768-775

Graham MC; Gavin KG, Kirika A and Farmer JG (2012) Processes controlling manganese distributions and associations in organic-rich freshwater aquatic systems: The example of Loch Bradan, Scotland. Science of the Total Environment 424, 239–250.

Gunier RB, Arora M, Jerrett M, Bradman A, Harley KG, Mora AM, Kogut K, Hubbard A, Austin C, Holland N, Eskenazi B. (2015) Manganese in teeth and neurodevelopment in young Mexican-American children. Environ Res. Oct;142:688-95

Haynes EN, Sucharew H, Kuhnell P, Alden J, Barnas M, Wright RO, Parsons PJ, Aldous KM, Praamsma ML, Beidler C, Dietrich KN. (2015) Manganese Exposure and Neurocognitive Outcomes in Rural School-Age Children: The Communities Actively Researching Exposure Study (Ohio, USA). Environ Health Perspect. 2015 Oct; 123 (10):1066-71

Haynes EN (2014) Childhood exposure to manganese and postural instability in children living near a ferromanganese refinery in Southeastern Ohio. Neurotoxicol Teratol. 2014 Jan-Feb;41:71-9.

Hernández-Bonilla D, Escamilla-Núñez C, Mergler D, Rodríguez-Dozal S, Cortez-Lugo M, Montes S, Tristán-López LA, Catalán-Vázquez M, Schilmann A, Riojas-Rodriguez H. (2016) Effects of manganese exposure on visuoperception and visual memory in schoolchildren. NeuroToxicology 57 (2016) 230–240

Homoncik SC, MacDonald AM, Heal KV, Dochartaigh BEO and Ngwenya BT (2010) Manganese concentrations in Scottish groundwater. Science of the Total Environment. 408, 2467-2473

Hong SB, Kim JW, Choi BS, Hong YC, Park EJ, Shin MS, Kim BN, Yoo HJ, Cho IH, Bhang SY, Cho SC. (2014) Blood manganese levels in relation to comorbid behavioral and emotional problems in children with attention-deficit/hyperactivity disorder. Psychiatry Res. 2014 Dec 15;220(1-2):418-25

Langley RL, Kao Y, Mort SA, Bateman A, Simpson BD, Reich BJ (2015) Adverse neurodevelopmental effects and hearing loss in children associated with manganese in well water, North Carolina, USA. J Environ Occup Sci. 2015;4(2):62-69

Lao Y, Dion LA, Gilbert G, Bouchard MF, Rocha G, Wang Y, Leporé N, Saint-Amour D. (2017) Mapping the basal ganglia alterations in children chronically exposed to manganese. Sci Rep. Feb 3;7:41804

Lin CC, Chen YC, Su FC, Lin CM, Liao HF, Hwang YH, Hsieh WS, Jeng SF, Su YN, Chen PC (2013) In utero exposure to environmental lead and manganese and neurodevelopment at 2 years of age. Environ Res. May;123:52-7

Liu J, Jin L, Zhang L, Li Z, Wang L, Ye R, Zhang Y, Ren A (2013) Placental concentrations of manganese and the risk of fetal neural tube defects. J Trace Elem Med Biol. Oct;27(4):322-5

Lucas EL, Bertrand P, Guazzetti S, Donna F, Peli M, Jursa TR, Lucchini R, and Smith DR, Impact of Ferromanganese Alloy Plants on Household Dust Manganese Levels: Implications for Childhood Exposure Environ Res. 138: 279–290.

Menezes-Filho JA, de O. Novaes C, Moreira JC, Sarcinelli PN, Mergler D (2011) Elevated manganese and cognitive performance in school-aged children and their mothers. Environmental Research 111 156-163

Menezes-Filho JA, Souza KOF, Rodrigues JLG, Santos NRD, Bandeira MJ, Koin NL, Oliveira SSDP, Godoy ALPC, Mergler D (2016) Manganese and lead in dust fall accumulation in elementary schools near a ferromanganese alloy plant. Environ Res. 2016 Jul; 148:322-329

Muñoz-Rocha TV, y Ortiz MT, Romero M, Pantic I, Schnaas L, Bellinger B, Claus-Henn B, Wright R, Wright RO, Téllez-Rojo MM. (2017) Prenatal co-exposure to manganese and depression and 24-months neurodevelopment. NeuroToxicology (article in press) available at: https://ac.els-cdn.com/S0161813X17301201/1-s2.0-S0161813X17301201-main.pdf?_tid=61b2d008-bf1f-11e7-b51c-00000aab0f6b&acdnat=1509552896_648bca17bef3e9e64ee0d2d0db5b9d0f (Accessed 2 November 2017)

Nascimento S, Baierle M, Göethel G, Barth A, Brucker N, Charão M, Sauer E, Gauer B, Arbo MD, Altknecht L, Jager M, Dias AC, de Salles JF, Saint' Pierre T, Gioda A, Moresco R, Garcia SC. (2016) Associations among environmental exposure to manganese, neuropsychological performance, oxidative damage and kidney biomarkers in children. Environ Res. 2016 May;147:32-43

Ode A, Rylander L, Gustafsson P, Lundh T, Källén K, Olofsson P, Ivarsson SA, Rignell-Hydbom A. (2015) Manganese and selenium concentrations in umbilical cord serum and attention deficit hyperactivity disorder in childhood. Environ Res. 2015 Feb;137:373-81

Oulhote Y, Mergler D, Barbeau B, Bellinger DC, Bouffard T, Brodeur M-E, Saint-Amour D, Legrand M, Sauvé S, and Bouchard MF (2014) Neurobehavioral Function in School-Age Children Exposed to Manganese in Drinking Water. Environ Health Perspect. 122(12):1343-50

Rahbar MH, Samms-Vaughan M, Dickerson AS, Loveland KA, Ardjomand-Hessabi M, Bressler J, Shakespeare-Pellington S, Grove ML, Pearson DA, Boerwinkle E. (2014) Blood manganese concentrations in Jamaican children with and without autism spectrum disorders. Environ Health. 2014 Aug 23;13:69

Rahman SM, Kippler M, Tofail F, Bölte S, Hamadani JD, Vahter M (2017) Manganese in Drinking Water and Cognitive Abilities and Behavior at 10 Years of Age: A Prospective Cohort Study. Environ Health Perspect. May 26; 125 (5) : 057003

Rink SM, Ardoino G, Queirolo EI, Cicariello D, Mañay N, Kordas K. Associations between hair manganese levels and cognitive, language, and motor development in preschool children from Montevideo, Uruguay. Arch Environ Occup Health. 2014;69(1):46-54.

Rodrigues EG, Bellinger DC, Valeri L, Hasan MO, Quamruzzaman Q, Golam M, Kile ML, Christiani DC, Wright RO, Mazumdar M (2016) Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. Environ Health. Mar 12;15:44

Rodríguez-Barranco M, Lacasaña M, Aguilar-Garduño C, Alguacil J, Gil F, González-Alzaga B, Rojas-García A. (2013) Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Sci Total Environ. Jun 1;454-455:562-77

Roth, JA (2006) Homeostatic and toxic mechanisms regulating manganese uptake, retention and elimination. Biology Research 39, 45-57.

Rugless F, Bhattacharya A, Succop P, Dietrich KN, Cox C, Alden J, Kuhnell P, Barnas M, Wright R, Parsons PJ, Praamsma ML, Palmer CD, Beidler C, Wittberg R, (2014) Childhood exposure to manganese and postural instability in children living near a ferromanganese refinery in Southeastern Ohio Neurotoxicology and Teratology 41 71–79

Sanders AP, Claus Henn B & Wright RO (2015) Perinatal and Childhood Exposure to Cadmium, Manganese, and Metal Mixtures and Effects on Cognition and Behavior: A Review of Recent Literature. Curr Envir Health Rpt (2015) 2:284–294

Shin DW, Kim EJ, Lim SW, Shin YC, Oh KS, Kim EJ. (2015) Association of hair manganese level with symptoms in attention-deficit/hyperactivity disorder. Psychiatry Investig. 2015 Jan;12(1):66-72

Skalny AV, Simashkova NV, Skalnaya AA, Klyushnik TP, Bjørklund G, Skalnaya MG, Tinkov AA (2017) Assessment of gender and age effects on serum and hair trace element levels in children with autism spectrum disorder. Metab Brain Dis. Oct;32(5):1675-1684

Torres-Agustín R, Rodríguez-Agudelo Y, Schilmann A, Solís-Vivanco R, Montes S, Riojas-Rodríguez H, Cortez-Lugo M, Ríos C. (2013) Effect of environmental

manganese exposure on verbal learning and memory in Mexican children. Environ Res. 2013 Feb;121:39-44.

WHO (2011) Manganese in Drinking water: Background document for the development of WHO guidelines for drinking water quality. Available at: http://www.who.int/water_sanitation_health/dwq/chemicals/manganese.pdf

Yu X, Chen L, Wang C, Yang X, Gao Y, Tian Y. (2016) The role of cord blood BDNF in infant cognitive impairment induced by low-level prenatal manganese exposure: LW birth cohort, China. Chemosphere. Nov;163:446-451

Yu XD, Zhang J, Yan CH, Shen XM. (2014) Prenatal exposure to manganese at environment relevant level and neonatal neurobehavioral development. Environ Res. 2014 Aug;133:232-8.

Zota AR, Riederer, AM, Ettinger AS, Schaider LA, Shine JP, Amarasiriwardena CJ, Wright RO and Spengler JD. Associations between metals in residential environmental media and exposure biomarkers over time in infants living near a mining-impacted site. J Expo Sci Environ Epidemiol. 26(5): 510–519.

Appendix 1

Literature search terms

In order to update our knowledge on manganese, we carried out a literature search using Pubmed for new data published since the good quality systematic review from 2013 by Rodríguez-Barranco *et al*.

Search terms:

Manganese toxicity
Manganese safety
Manganese in drinking water, UK
Manganese in soil, UK
Manganese in breastmilk
Manganese in house dust
Manganese, Children

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from manganese in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible manganese exposure from dietary sources in children aged 4 to 18 months

Two surveys were conducted during 2014 which measured the concentrations of elements in food consumed by infants (4 to 18 months) and young children (18 months to 5 years). The first survey was a survey on types of foods eaten by infants (referred to as the Infant Metals Survey), the other was a total diet study (TDS) which focused on sampling foods eaten by young children. Both studies measured the concentrations of manganese.

The Infant Metals Survey measured the concentrations of metals and other elements in food 'as sold', in the following categories: infant formula (Table A1) commercial infant foods (Table A2), and groups of food comprising the top 50 most commonly consumed varieties of foods not specifically marketed for infants (Table A3). The results from this survey were used together with food consumption data from the Diet and Nutrition Survey for Infants and Young Children (DNSIYC) (DH, 2013) to estimate dietary exposures for children aged 4 to 18 months.

The TDS consisted of: (i) selecting foods based on food consumption data, to represent as best as possible a typical diet; (ii) their preparation to food as consumed and (iii) the subsequent pooling of related foods before analysing the composite samples for elements. The concentrations of 26 elements, including manganese, were measured in the 2014 TDS. The composite samples for 27 food groups (Table A4) were collected from 24 UK towns and analysed for their levels of manganese and other elements. Where appropriate, tap water was used in the preparation and cooking of food samples. The results from this survey were also used together with food consumption data from the DNSIYC (DH, 2013) to estimate dietary exposures for children aged 4 to 18 months.

Table A1. Infant formula

Infant Formula	
Dry Powder	**Made Up Formula**
First and Hungrier Milk	First Milk and Hungrier Milk
Follow On Milk	Follow On milk
Growing Up Milk	Growing up Milk
Soy Milk	
Goat Milk	

Organic Milk	
Comfort Milk	

Table A2. Commercial infant foods

Commercial Infant Foods
Cereal Based Foods and Dishes
Dairy Based Foods and Dishes
Fruit Based Foods and Dishes
Meat and Fish Based Foods and Dishes
Snacks (Sweet and Savoury)
Other Savoury Based Foods and Dishes (excluding Meat)
Drinks

Table A3. Other foods commonly eaten by infants.

Other Foods	
Beverages	Fruit Products
Bread	Green Vegetables
Canned Vegetables	Meat Products
Cereals	Milk
Dairy Products	Other Vegetables
Eggs	Potatoes
Fish	Poultry/Chicken
Fresh Fruit	

Table A4. The 27 food groups used for analysis of 26 elements in the 2014 TDS

TDS Food Groups*	
Bread	Fresh Fruit
Miscellaneous Cereals	Fruit Products
Carcase Meat	Non Alcoholic Beverages
Offal	Milk
Meat Products	Dairy Products
Poultry	Nuts
Fish	Alcoholic Drinks
Fats and Oils	Meat Substitutes
Eggs	Snacks
Sugars	Desserts
Green Vegetables	Condiments

Potatoes	Tap Water
Other Vegetables	Bottled Water
Canned Vegetables	

*Food samples representative of the UK diet are purchased throughout the year in 24 towns covering the UK and 137 categories of foods are combined into 27 groups of similar foods for analysis

Exposure Assessments

Infant Metals Survey

Tables A5, A6 and A7 summarise lower- (LB) and upper-bound (UB) total dietary exposures to manganese calculated using results from the infants Metal Survey for ages 4 to 18 months.

Table A5: Estimated manganese exposure from infant formula in children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Infant Formula - Manganese LB to UB (ug/kg bw/day)									
	4 to <6m		6 to <9m		9 to <12m		12 to <15m		15 to 18m	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Comfort	0	0	0.012	0	0.044	0	0	0	0	0
Dry First Milk_ From Birth	0.033	0.68	0.048	0	0.013	0	0	0	0	0
Dry Follow On_ 6 Months	0	0	0.029	0	0.051	0.35	0.0026	0	0.0067	0
Dry_ Growing Up Milk_ 12 months	0	0	0.000	0	0	0	0.017	0	0.0060	0
Goat Milk Formula	0	0	0.024	0	0	0	0	0	0	0
Hipp Organic	0	0	0.013	0	0.0073	0	0.0023	0	0	0
Soy	0.047-0.31	0	0.023-0.16	0	0.024-0.16	0	0.0069-0.046	0	0.0041-0.028	0
Wet_ First Milk_ From Birth	3.6	8.8	1.5	6.6	0.64	4.1	0.094	1.8	0.022	0
Wet_ Follow on_ 6 Months	0.55	5.7	2.0	6.9	1.9	6.2	0.47	4.0	0.24	2.6
Wet_ Growing up Milk_ 12 months	0	0	0.0032	0	0.051	0	0.45	3.6	0.29	2.8
TOTAL	**4.2-4.5**	**8.8-8.9**	**3.6-3.8**	**7.8-8.2**	**2.8-2.9**	**6.5-6.6**	**1.0-1.1**	**4.6**	**0.57-0.60**	**3.4-3.5**

Table A6: Estimated manganese exposure from commercial infant foods in children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Infant Formula - Manganese LB to UB (ug/kg bw/day)									
	4 to <6m		6 to <9m		9 to <12m		12 to <15m		15 to 18m	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Cereal based foods and dishes	4.0	19	4.6	23	3.3	21	1.4	14	0.54	6.1
Dairy based foods and dishes	1.0	10	1.0	9.5	0.65	6.8	0.34	4.7	0.12	1.9
Fruit based foods and dishes	4.3	33	6.3	36	6.0	32	3.8	27	2.3	20
Meat and fish based foods and dishes	2.5	16	4.1	21	3.9	20	2.3	16	1.2	9.4
Not applicable_ drinks	0.30	3.0	0.39	4.0	0.34	3.0	0.17	2.5	0.15	1.8
Other Savoury Based foods and dishes_ no meat	2.0	13	2.8	16	3.0	21	1.2	12	0.59	8.9
Snacks sweet and savoury	5.0	31	7.4	38	7.3	39	5.3	35	3.3	21
TOTAL	**19**	**81**	**27**	**85**	**24**	**91**	**14**	**65**	**8.2**	**42**

Table A7: Estimated manganese exposure from other foods commonly eaten by children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Infant Formula - Manganese LB to UB (ug/kg bw/day)									
	4 to <6m		6 to <9m		9 to <12m		12 to <15m		15 to 18m	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Beverages	0.0036-0.0042	0.055-0.064	0.010	0.079-0.092	0.0076-0.0088	0.10-0.12	0.0065-0.0075	0.076-0.089	0.0093-0.011	0.16-0.18
Bread	0.55	7.9	5.1	33	14	57	22	72	24	80
Canned Vegetables	0.18	2.3	0.83	8.8	2.0	14	3.0	17	2.6	12
Cereal	0.84	10	14	77	21	94	26	110	32	110
Dairy Products	0.26-0.27	1.5-1.6	0.54	2.3-2.4	0.66-0.69	2.5-2.6	0.67-0.69	2.4-2.5	0.61-0.63	2.1
egg	0.0057	0.0062	0.058	0.60	0.12	0.92	0.39	1.9	0.35	1.8
Fish	0.019	0.11	0.14	1.3	0.30	2.0	13	47	16	48
Fresh Fruit	3.3	23	6.5	30	9.8	40	0.36	3.4	0.52	3.9
Fruit Products	0.14	2.3	0.22	2.3	0.22	2.2	1.8	8.6	1.8	8.9
Green Vegetables	0.76	6.5	1.6	7.7	1.8	12	0.68	4.6	0.91	7.5
Meat Products	0	0	0.14	2.4	0.34	3.2	0.41	1.2	0.41	0.99
Milk	0.0070	0.078	0.039	0.21	0.10	0.81	4.0	17	3.9	15
Other Vegetables	4.8	35	6.4	30	5.8	25	3.7	16.24	3.3	13
Potato	1.1	7.7	2.5	11	3.4	14	0.033	0.19	0.031	0.20
Poultry or Chicken	0.0081	0.053	0.024	0.19	0.032	0.23	0.19	1.2	0.20	1.2
TOTAL	**12**	**59**	**38**	**130**	**60**	**150**	**76**	**170**	**87**	**170**

Total Diet Study

Table A8 summarise lower- and upper-bound total dietary exposures to manganese calculated using the 2014 TDS for ages 12 to 18 months. The data for each food category is reported separately so that the contribution to exposure from each class could be assessed more transparently for the most relevant infant age group. In addition the total exposure from the diet has also been provided.

Table A8 Estimated manganese exposure from food eaten by young children aged 12 months to 18 months using data from the TDS Groups

Food Groups	Total Diet Study - Manganese LB to UB (ug/kg bw/day)			
	12m to <15m		15m to <18m	
	Mean	97.5th Percentile	Mean	97.5th Percentile
Bread	20	54	22	60
Miscellaneous Cereals	38	120	46	140
Carcase meat	0.084	0.43	0.10	0.52
Offal	0.0066	0	0.049	0
Meat products	1.3	6.6	1.5	7.1
Poultry	0.43	1.9	0.48	2.1
Fish	0.94	4.3	0.88	4.5
Fats and oils	0.0024	0.0096	0.0028	0.010
Eggs	0.23	1.2	0.23	1.2
Sugars	0.61	3.7	0.92	4.6
Green vegetables	1.8	8.1	2.0	7.6
Potatoes	5.5	20	5.1	17
Other vegetables	5.8	21	5.8	19
Canned vegetables	2.8	14	2.8	13
Fresh fruit	8.9	31	11	31
Fruit products	4.2	30	4.8	32
Non-alcoholic beverages	26	120	31	150
Milk	0.24	0.67	0.24	0.57
Dairy products	3.1	16	2.6	11
Nuts	1.4	5.9	0.63	5.7
Alcoholic drinks	0.0034	0.021	0.0016	0
Meat substitutes	0.35	0	0.96	12
Snacks	0.60	4.1	0.93	6.5
Desserts	0.53	4.6	0.73	5.3
Condiments	0.59	3.5	0.67	3.4
Tap water	0-0.020	0-0.075	0-0.17	0-0.67
Bottled water	0-0.0077	0-0.067	0-0.0014	0-0.021
Total	**120**	**280**	**140**	**290**

Results reported to 2 SF

References

DH (Department of Health) (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from manganese in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible manganese exposure from dietary sources in young children aged 18 to 60 months

A Total Diet Study (TDS) was conducted during 2014 which measured the concentrations of manganese by young children (18 months and older).

The TDS consisted of: (i) selecting foods based on food consumption data, to represent as best as possible a typical diet; (ii) their preparation to food as consumed and (iii) the subsequent pooling of related foods before analysing the composite samples for elements. The concentrations of 26 elements, including manganese, were measured in the 2014 TDS. The composite samples for 27 food groups (Table B1) were collected from 24 UK towns and analysed for their levels of manganese and other elements. Where appropriate, tap water was used in the preparation and cooking of food samples. The results from this survey were also used together with food consumption data from years 1 to 4 of the National Diet and Nutrition Survey Rolling Programme (NDNS) (Bates *et al.,* 2014) to estimate dietary exposures for young children aged 18 months to 5 years.

Table B1. Food groups used for analysis of 26 elements in the 2014 TDS

TDS Food Groups*	
Bread	Fresh Fruit
Miscellaneous Cereals	Fruit Products
Carcase Meat	Non Alcoholic Beverages
Offal	Milk
Meat Products	Dairy Products
Poultry	Nuts
Fish	Alcoholic Drinks
Fats and Oils	Meat Substitutes
Eggs	Snacks
Sugars	Desserts
Green Vegetables	Condiments
Potatoes	Tap Water
Other Vegetables	Bottled Water
Canned Vegetables	

*Food samples representative of the UK diet are purchased throughout the year in 24 towns covering the UK and 137 categories of foods are combined into 27 groups of similar foods for analysis

Exposure Assessment

Table B2 summarises lower- and upper-bound total dietary exposures to manganese calculated using the 2014 TDS for young children aged 18 months to 5 years. The data for each food category is reported separately so that the contribution to exposure from each class could be assessed more transparently for the most relevant infant age group. In addition the total exposure from the diet has also been provided.

Table B2. Estimated manganese exposure from food eaten by young children aged 18 months to 5 years using data from the TDS Groups

	Total Diet Study - Manganese LB to UB (ug/kg bw/day)			
	18 to <24		24 to <60	
FOOD GROUP	Mean	97.5th Percentile	Mean	97.5th Percentile
Bread	23.39	52.58	26.63	61.92
Miscellaneous Cereals	49.31	103.3	40.29	101.92
Carcase meat	0.11	0.59	0.07	0.37
Offal	0.01	0	0.02	0
Meat products	1.84	8.49	2.24	7.44
Poultry	0.56	1.58	0.47	2.02
Fish	1.16	4.64	0.89	3.41
Fats and oils	0	0.01	0	0.01
Eggs	0.17	0.98	0.18	1.02
Sugars	1.08	5.11	1.55	6.53
Green vegetables	1.72	10.3	1.77	7.19
Potatoes	5.23	11.03	4.76	13.92
Other vegetables	3.53	11.79	3.68	13.14
Canned vegetables	4.71	18.07	2.9	11.21
Fresh fruit	13.34	34.98	9.64	25.4
Fruit products	10.8	41.73	9.84	47.43
Non-alcoholic beverages	41.68	172.22	40.17	116.52
Milk	0.22	0.7	0.16	0.45
Dairy products	2.81	13.38	1.57	6.28
Nuts	0.33	0.47	1.02	14.23
Alcoholic drinks	0	0	0	0
Meat substitutes	0.25	4.24	1.08	16.45
Snacks	1.1	6.63	1.27	6.7
Desserts	1.11	6.08	1.24	5.92
Condiments	0.47	2.32	0.73	3.84
Tap water	0-0.02	0-0.12	0-0.02	0-0.08
Bottled water	0	0-0.01	0	0-0.02
Total	165	280	152	267

References

Bates, B.; Lennox, A.; Prentice, A.; Bates, C.; Page, P.; Nicholson, S.; Swan, G. (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf