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

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

Introduction

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. 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]. At the time, a full literature search had not been carried out to update the toxicological database. This has now been completed hence the current COT review on manganese.

3. No Reference Nutrient Intake (RNI) has been set for manganese as there were only 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

4. 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).

5. 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 been documented only under experimental conditions, where decreased levels of cholesterol and clotting proteins were recorded. Black hair was found to redden, fingernail growth slowed and scaly dermatitis was observed (EVM, 2003).

[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

6. A chronic excess of manganese has been found to produce a range of neurological signs and symptoms in humans which combine, in severe cases to form a Parkinson disease-like syndrome called Manganism. Primary effects 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)

7. 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.

8. 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.

9. The WHO established a TDI of 60 µg/kg body weight 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 speciation was taken into account, if at all, in establishing this reference dose. Based on this TDI, the WHO set a health-based guidance value for water of 400 µg/L.

10. A number of HBGVs for chronic exposure to manganese 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).

[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

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

Sources of manganese exposure

Human breast milk

11. 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).

12. 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 µg/L SD 3.9) and the lowest levels found in Turin (13.8 µg/L 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).

13. A median concentration of 6.3 µg/kg was reported for manganese in breast milk, based on the pooled samples of breast milk donated by 27 healthy mothers in Austria (Krachler et al, 2000).

14. According to EFSA, average manganese concentrations in breast milk throughout Europe 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

15. 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). More details can be found in paragraphs 25-27.

Drinking water

16. 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, which is based on this effect, is set below any expected HBGV.

17. 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

18. 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 from dust, as well as soil, in this assessment.

Air

19. 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 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

20. 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.

21. 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, where individual bodyweight data were not available

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

22. No UK 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 breast milk. 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).

23. 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 in breast milk in the range reported by EFSA, 2013 (paragraph 14). 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.

24. 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

	Manganese 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

25. Manganese exposure estimates for infant formulae and complementary foods were derived using occurrence data from the Infant Metals Survey (FSA, 2016a). 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.

26. 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 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.

27. 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

28. 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. Estimated mean and 97.5th percentile exposures to manganese from a combination of all food groups were up to 140 and 290 µg/kg bw/day, respectively (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.

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

29. 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 18) (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.

30. The estimated 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	Manganese Exposure (µg/kg bw/day)					
	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

31. 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

32. 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/m^3, respectively, from monitoring sites in the UK (see paragraph 19). 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 concentration (ng/m^3)	Manganese Exposure (µg/kg bw/day)							
	Ages (months)							
	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

33. 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 some sources, only about 5% of dietary manganese is actually absorbed by the GI tract - 5.9 +/- 4.8%; range 0.8-16% (Davidsson et al, 1989). Another study looked at absorption of labelled manganese from different food matricies - mean absorption: lettuce 5.2%, spinach 3.81%, sunflower seeds 1.71%, wheat 2.16%, $MnCl_2$ 8.9% (Johnson et al, 1991).

34. Once manganese has entered into the circulation, it accumulates primarily in the liver (1.2-1.3 mg/kg), brain (0.15-0.46 mg/kg) and bone (from 1 mg/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).

35. Manganese is primarily excreted via the faeces through the hepatobiliary route. Small amounts are excreted via the urine and much lower amounts through breast milk and sweat.

Human studies and case studies with excess manganese

36. 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 was 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).

37. 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.

38. A further review looking at cadmium, manganese and metal mixture exposure in early life and effects on cognition and behaviour concluded 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).

39. 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 to assess exposure. 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 stated 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 The authors conclude that research to identify biomarkers feasible for use in fetuses and infants is urgently needed given their unique vulnerability to excessive manganese (Coetzee et al, 2016).

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

41. 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).

42. A table outlining the studies published since the review by Rodrigues-Barranco et al, 2013 can be found in Annex A at the end of this paper.

Risk characterisation

44. There appears to be a significant amount of literature indicating a link between elevated manganese exposure and neurodevelopmental effects in children. However, the findings are not entirely consistent, for example, whether males or females are differentially affected. 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). Interpretation is complicated by the non-monotonic (U-shaped) relationship between manganese exposure and neurodevelopment, such that both low and high exposure to manganese can have a negative effect.

45. 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.

46. The WHO established a TDI of 60 µg/kg body weight in the Guidelines for Drinking Water Quality (WHO, 2011). This was based on the upper range intake of 11 mg/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 15 mg/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 exposures calculated for UK infants and children have been compared with the WHO TDI. Table 10 below compares estimated exposures at different age ranges and shows that a number of groups could 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 could all exceed the TDI established by the WHO.

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

		Manganese Exposure (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:

47. The Committee concluded that there was evidence that excessive exposure to manganese was associated with adverse effects on neurodevelopment in young children. Exposure was primarily 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 and by socioeconomic factors.

48. Members stated that whilst the number of studies 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 on the effects of current dietary exposures to manganese on neurodevelopment. More evidence is necessary to draw conclusions on any such relationship.

49. Members noted the use of several different biomarkers to determine manganese exposure in the recently published literature, including concentrations in 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.

50. 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. As exposure of infants and young children to manganese is almost entirely via the diet, it could be argued that this correction factor is not necessary for the risk characterisation in these groups.

51. 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, although any risk at current dietary exposures is likely to be low.

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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 (Rodrigues-Barranco et al, 2013)

Search terms:

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

ANNEX A

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

Table C1 Studies on manganese

Biomarker	Participants	Measure of Neurological function	Results	Reference
Case-control studies				
Water Mn concentration	10 children aged 9-15 years and 13 age-matched controls	MRI images of brain structures	High-manganese exposed group showed slightly enlarged putamen, globus pallidus and 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 showed 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 impairment of motor performance ($p < 0.05$)	Lao et al, 2017
Cord blood	166 children with ADHD and age-	Diagnosis of ADHD	Mn in cord blood not associated with a diagnosis of ADHD before or after adjusting for confounders.	Ode et al, 2015

	matched controls; Malmo Sweden		Mn/selenium ratio was also not associated with ADHD diagnosis (p=0.81)	
Hair Mn	40 children aged 6-15 with ADHD and 43 controls, Seoul, South Korea	Diagnosis of ADHD; intelligence test: Weschsler Intelligence Scale for Children, 3rd edition (WISC-III)	After controlling for confounders including age and sex, higher hair Mn concentrations were significantly associated with ADHD (OR=6.40, 95% CI=1.39–29.41, p=0.017)	Shin et al, 2015
Blood samples	109 children aged 2-8 years with autistic spectrum disorders and age-matched controls; Jamaica	Children with confirmed diagnosis of autistic spectrum disorders; questionnaire to assess demographic and socioeconomic information, medical history and potential Mn exposure. General Linear Models (GLM) were used to test the association between blood Mn and ASD	In univariable GLM no significant association between blood Mn 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 Mn and ASD status, (11.5 µg/L for cases vs. 11.9 µg/L for controls; p = 0.48)	Rahbar et al, 2014
Hair and blood Mn concentration	79 children aged 7-11 years and 95 age-matched controls; Mexico	Children's Auditory Verbal Learning Test (CAVLT)	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 Mn 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 Mn levels showed a negative but non-significant association with the CAVLT scores	Torres-Agustín et al, 2013

Placenta Mn, iron, copper, zinc and selenium	80 infants with neural tube defects and 50 controls; northern China	Diagnosis of a neural tube defect	The median Mn 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. There was a clear positive dose-response relationship between concentrations of Mn and risk of neural tube defects ($p < 0.05$). 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
Cross-sectional studies				
Hair manganese and blood lead	70 children aged 7-12 living within 3.5 km of a ferro-manganese alloy plant.	Sociodemographic questionnaire, battery of tests including tests to assess inhibition, word generation, list memory, motor function; Conner's Abbreviated Teacher Rating Scale.	Elevated hair Mn were associated with lower performance in verbal memory, as measured by the free recall after interference ($\beta = -1.8$; 95% CI: – 3.4, – 0.2), which indicates susceptibility to interference, and Delayed Effect ($\beta = -2.0$; 95% CI: –3.7, – 0.2), representing a loss of information over time. Additionally, we found patterns of effect modification by sex in three subtests measuring verbal memory: the free recall after interference score, Interference Effect, and Delayed Effect (all at $p < 0.10$)	Carvalho et al, 2018
Blood lead (Pb) and manganese (Mn) in hair and toenails	225 children aged 7-12 years from 4 schools in an industrial region of Brazil near a ferro-manganese alloy plant	Child and maternal IQs were estimated using the Wechsler Abbreviated Scale for Intelligence (WASI)	After adjusting for maternal IQ, age and Mn exposure, child IQ drops by 8.6 points for a 10-fold increase in blood lead levels. Moreover, an effect modification of Mn co-exposure was observed. In children with low toenail Mn, association between Pb and child IQ was not significant ($\beta = -6.780$, $p = 0.172$). However, in those with high toenail Mn, the association was increased by 27.9% ($\beta = -8.70$, $p = 0.036$). Low	Menezes-Filho et al, 2018

			Pb exposure is associated with intellectual deficit in children, especially in those with high toenail Mn.	
Blood lead (PbB) and blood manganese (MnB) and manganese in hair (MnH) and toenails (MnTn)	165 children aged 7-12 years from 4 schools in an industrial region of Brazil near a ferro-manganese alloy plant	Children's behaviour was assessed with the Child Behaviour Check List (CBCL) reported by parents	MnH and MnB were not associated with any scale of the CBCL behaviour scores. Found a positive association between logMnTn and raw total CBCL score ($\beta = 10.17$, $p = 0.034$), adjusting for sex, age, maternal IQ and logPbB. Analyses using Generalized Additive Model showed non-linear associations between MnTn and externalizing behaviour ($p = 0.035$), as well as with the related subscales: aggressive behaviour ($p = 0.045$) and rule-breaking behaviour ($p = 0.024$). Further positive associations were observed between MnTn and thought problems ($p = 0.031$) and social problems ($p = 0.027$)	Rodrigues et al, 2018
Deciduous teeth	142 children aged 11-14 living in the proximity of a ferro-Mn plant; Italy	Virtual Radial Arm Maze to measure visuospatial learning and memory	A U-shaped curve observed in females for prenatal exposure and results for time taken to complete the task and the number of errors made. No effects observed in males or for postnatal exposure	Bauer et al, 2017
Water, hair, toe nail and saliva Mn concentrations	259 children aged 6-13; New Brunswick, Canada	Each child completed 4 sub-tests of the Wechsler Intelligence scale for Children (4^{th} edition). IQ.	In girls, higher Mn 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 Mn, β -5.65, 95% CIs: 10.97, 0.32). Opposite associations were observed in boys: better Performance IQ scores with higher Mn concentration in 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 Mn exposure indicators	Bouchard et al, 2018

Maternal and cord blood Mn	541 mother-infant pairs; Mexico	Child neurodevelopment assessed at 24 months of age using the Bayley Scales of infant and toddler neurodevelopment by blinded psychologists. Mothers assessed for depression during the third trimester	Mean cord blood and maternal blood Mn concentrations were 50.1 (SD 16.5) μg/L and 27.7 (SD 8.7) μg/L. An increase in maternal blood Mn 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 establish whether there is a significant association between Mn exposure, depression and child development	Muñoz-Rocha et al, 2017
Water Mn	1265 children aged 10 years	Cognitive abilities assessed using the Wechsler Intelligence scale for Children IV and a Strengths and Difficulties Questionnaire	The median water Mn was 0.20 mg/L (range 0.001–6.6) during pregnancy and 0.34 mg/L (<0:001–8:7) at 10 y. In children with low arsenic exposure; cognitive abilities were not associated with Mn exposure. Interaction between gender and water Mn 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 Mn (<3 mg/L) was positively associated with cognitive ability measures in girls but not in boys. Water Mn 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 Mn was associated with a decreased risk of emotional problems [odds ratio (OR) =0.39 (95% CI: 0.19, 0.82)] in boys. In girls,	Rahman et al, 2017

			water Mn was mainly associated with low prosocial scores [prenatal W-Mn: OR=1.48 (95% CI: 1.06, 1.88)]. Water Mn consumed at 5 and 10 years of age did not have an effect on cognitive abilities and behaviour	
Hair Mn	267 children aged 7-11; Mexico	Rey-Osterrieth complex figure test - a complex figure is copied then drawn again from memory	Mean hair Mn was found to be 9 times higher in the mining region compared to the control region. Hair Mn 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
Hair Mn	83 children as above	Hair Mn was plotted against distance from the plant	Mean hair Mn from exposed (<1.8 km 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
Blood, hair and drinking water Mn concentration	63 children aged 6-12 years; Southern Brazil	Neuropsychological functions assessed included attention, perception, working memory, phonological awareness and inhibition. Intelligence quotient (IQ) was also evaluated. Biomarkers of oxidative stress and kidney function were also assessed	Mn 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 Mn and visual attention (β = 0.649; p<0.001), visual perception and phonological awareness. Hair Mn was inversely associated with working memory, and water Mn was associated with 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	Nascimento et al, 2016

			(p<0.05). Significant associations were found between blood, hair and water Mn levels and biomarkers of oxidative damage and kidney function and between some oxidative stress biomarkers and neuropsychological tasks (p<0.05)	
Water lead, arsenic and Mn	524 infants and their mothers; Bangladesh	Neurodevelopmental assessment: Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III).	Water Mn concentrations appeared to correlate with fine motor scores (β2Ln water Mn = −0.08, SE = 0.03, p = 0.02). The authors conclude that at levels of <400 µg/L in water, Mn is beneficial to fine motor development but at higher levels Mn can be detrimental	Rodrigues et al, 2016
Hair Mn	93 children from a mining region of Ecuador	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	Having controlled for age and educational level, children with elevated levels of hair Mn (over 2 µg/g) had poor performance in neurobehavioral tests. Children with elevated levels of Mn in the river water (970 µg/L) were the ones who had the highest levels of hair Mn and the worst performance in neurobehavioral tests (no p-values supplied)	Betancourt et al, 2015
Maternal blood Mn	265 mother-infant pairs; South Korea	Neurodevelopmental testing using the Bayley Scales of Infant Development II (BSID-II) at 6 months of age	Arithmetic mean maternal blood Mn 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 authors observed no significant sex differences in BSID-II. Children from the group with maternal blood Mn of 25.0–	Chung et al, 2015

			29.9 µg/L demonstrated higher 6-month neurodevelopmental scores (MDI and PDI) compared with children in the highest Mn group (≥ 30.0 µg/L) and the lowest Mn group (< 20 µg/L)	
Deciduous teeth	193 children assessed at 6-, 12- and 24 months; California, USA	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 Mn 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 Mn exposure and PDI at 6-months was observed. A significant interaction between postnatal Mn 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 Mn 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 Mn 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
Blood and hair Mn and lead.	404 children aged 7-9; Ohio, USA	IQ	Geometric mean blood (n = 327) and hair Mn (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 Mn concentrations were associated with	Haynes et al, 2015

			lower Full-Scale IQ and subscale scores, with significant negative associations between the highest quartile and middle two quartiles of blood Mn (β –3.51; 95% CI: –6.64, –0.38; p = 0.041) and hair Mn (β –3.66; 95% CI: –6.9, –0.43%; p = 0.01) and Full-Scale IQ	
Blood lead and Mn and urinary cotinine	1089 children aged 8-11 years; South Korea	Battery of tests designed to assess IQ, attention, academic functions, emotional and behavioural problems	Median blood Mn was 14.14 µg/L. After adjusting for urine cotinine, blood lead, children's IQ, and other potential confounders, the high Mn 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 Mn group showed lower colour scores in the Stroop test (B=−3.24, p=0.040)	Bhang et al, 2014
Blood Mn	890 children	Children assessed for ADHD, emotional and behavioural problems and IQ	A significant interaction was identified between ADHD status and blood Mn concentration in predicting scores for anxiety/depression (p = 0.015), social problems (p = 0.005), delinquent (p = 0.033) and aggressive behaviour (p = 0.002), internalising (p = 0.013) and externalising problems (p = 0.003). No associations were found in children without ADHD	Hong et al, 2014
Water, hair, toe nail and saliva Mn concentrations	259 children aged 6-13; New Brunswick, Canada	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 Mn was associated with a significant reduction in scores for memory and attention (–24% (95% CI: –36, –12%) for memory and –25% (95% CI: –41, –9%) for attention)	Oulhote et al, 2014

Hair Mn and lead	60 children aged 14-45 months; Montevideo, Uruguay	Bayley Scales of Infant Development III.	Mean hair Mn 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 Mn and BSID scores, with girls having lower scores relating to Mn than boys. After adjustment for confounders, no relationships were found between hair Mn and BSID scores except when stratified by sex, boys having a positive association between hair Mn and language scores (no p-values provided)	Rink et al, 2014
Hair and blood Mn and lead concentrations	55 children aged 7-9; Ohio, USA	Postural balance assessment	Hair and blood Mn 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 Mn exposure and low-level blood lead are significantly associated with poor postural balance (p-values not given)	Rugless et al, 2014
Hair and blood Mn and blood lead concentrations	83 children aged 6 to 11 years 11 months living near a ferro-Mn plant	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 Mn 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 Mn was 3.50 µg/g (0.10–77.45) and correlated to children's hair Mn levels. Child and care-givers cognitive performance scores were negatively associated with elevated hair Mn ($p < 0.05$). No such correlations were observed for blood Mn	Menezes-Filho et al, 2011
Hair	46 children aged 6-15 years; Quebec, Canada	Measures of hyperactivity (Revised Conners' Rating Scale for parents and teachers on sub-scales for Oppositional, Hyperactivity, Cognitive	Elevated hair Mn was significantly associated with higher scores for oppositional ($p = 0.02$) and hyperactivity ($p = 0.002$) behaviours	Bouchard et al, 2007

		Problems/Inattention and ADHD).		
Cross sectional studies (including food frequency questionnaire)				
Hair and water Mn; food frequency questionnaires	362 Children aged 6-13 years; Quebec, Canada	IQ	Hair Mn levels correlated with water Mn levels but did not correlate with estimated dietary intake. Elevated water Mn and hair Mn levels were significantly associated with lower IQ scores with a 10-fold increase in exposure from water equating to a decrease in 2.4 IQ points after adjusting for confounders (95% confidence interval, -3.9 to -0.9, p = <0.01)	Bouchard et al, 2011
Nested cohort studies				
Hair manganese concentration	287 children from Quebec, Canada	IQ test at adolescence	Higher Mn concentration in water measured at follow-up was associated with lower Performance IQ in girls (β for a 10-fold increase = −2.8, 95% confidence intervals [CI] −4.8 to −0.8) and higher Performance IQ in boys (β = 3.9, 95% CI 1.4 to 6.4). IQ scores were not significantly associated with Mn concentration in hair, although similar trends as for concentration in water were observed. For children whose Mn concentration in water increased between baseline and follow-up, Performance IQ scores decreased significantly (intra-individual difference, −2.4 points)	Dion et al, 2018
Urinary ethylenethiourea (a metabolite of Mancozeb, a fungicide containing manganese)	355 one year old infants living near banana plantations in Costa Rica	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	In girls, higher metabolite levels were associated with lower social and emotional scores. In boys, higher hair manganese levels were associated with lower social and emotional scores [β per 10-fold increase=-7.4 points (95% CI: -15.2, 0.4)], whereas higher hair Mn was associated with lower cognitive scores [-3.0 (-6.1, 0.1)]. Among boys,	Mora et al, 2018

			higher hair Mn was associated with lower social-emotional scores [-4.6 (-8.5, -0.8)]. We observed null associations for blood Mn, language, and motor outcomes. P values not supplied.	
Deciduous teeth	194 children aged 11-14; Italy	Body stability (mean sway, transversal sway, sagittal sway, sway area and sway intensity)	Higher prenatal Mn exposure was associated with better body stability in boys but was inversely associated with these parameters in girls ($p < 0.05$). Higher prenatal Mn was also associated with better hand/finger co-ordination and hand/eye co-ordination in boys compared to girls (not statistically significant)	Chiu et al, 2017
Well water Mn, arsenic and lead concentration	Children with hearing loss, delayed milestones or speech and language disorders from a large cohort of 17000; North Carolina, USA	Mn arsenic and lead measured in well water samples and compared to the location of children with hearing loss, delayed milestones and speech and language disorders	The mean county concentration of Mn 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 Mn concentration. The mean county arsenic and lead concentrations were not associated with the prevalence of delayed milestones. An increase in the mean county Mn 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 Mn concentration (no p-values supplied)	Langley et al, 2015

Cord blood Mn, arsenic, lead and mercury	230 mothers and infants; Taiwan	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 Mn were 47.90 mg/L (range, 17.88–106.85 mg/L). After adjusting for confounders, Mn 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
Cohort studies				
Maternal blood sampled in 2nd and 3rd trimester	15 children aged 6-7; Mexico	Resting state functional magnetic resonance imaging	Maternal blood Mn concentrations ranged from 2.7 – 41.1 µg/L. Families consented to functional magnetic resonance imaging (fMRI). Children exposed to higher maternal blood Mn 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. Higher prenatal Mn was associated with reduced functional connectivity between the right globus pallidus and the inferior frontal gyrus (all $p < 0.05$)	De Water et al, 2018
Dentine biomarkers of Mn, Pb and Zn from all deciduous teeth	133 children from Mexico City	Behaviour at ages 8-11 years of age using the Behaviour Assessment System for Children, 2nd edition (BASC-2)	Prenatal exposure to Mn protective against behavioural problems; post-natal exposure was associated with an increase in internalising behaviour problems such as anxiety ($p < 0.05$)	Horton et al, 2018
Blood and hair manganese and lead levels	106 children aged 7-9 years	IQ (Weschsler Abbreviated Scale of Intelligence)	In the single biomarker model, increasing log hair Mn was significantly associated with declines in Full Scale IQ, processing speed and working memory. In the sex-stratified models, although the associations between hair Mn and WISC-IV outcomes were not statistically significant, a	Haynes et al, 2018

			similar trend was observed between hair Mn concentration and Full Scale IQ for both female (−2.24, 95% CI: −4.88, 0.39) and male (−1.55, 95% CI: −4.20, 1.10). In the multiple biomarkers model, the association between log hair Mn and WISC-IV outcomes was no longer statistically significant. There was no association between log blood Mn, log blood Pb, log serum cotinine, and WISC-IV outcomes, except log serum cotinine was positively associated with verbal comprehension in the multiple biomarkers model	
Maternal and cord blood samples	224 mother-infant pairs Oklahoma USA	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 Mn (10.1 µg/L) was associated with a 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) ($p < 0.05$). Cord blood was not associated with mental and psychomotor development indices	Claus-Henn et al, 2017
Cord blood Mn and brain-derived neurotrophic factor	377 mothers and their infants; China	Neurodevelopmental assessment at 12 months: Gesell Developmental Inventory (GDI) and maternal non-verbal intelligence using the Raven's Progressive Matrices Test. GDI has	After adjusting for confounding factors, serum Mn level was significantly associated with gross motor scores ($\beta = -6.0$, 95% CI: -11.8 to -0.2, $p < 0.05$) and personal/social scores ($\beta = -4.2$, 95% CI: -8.4 to 0.1 $p < 0.05$). BDNF level was positively correlated with personal/social score ($\beta = 0.7$, 95% CI: 0-1.4, $p < 0.05$). A significant correlation was found between Mn and BDNF ($r = - 0.13$, 95% CI: -0.23 to -0.03, $p < 0.01$). Furthermore, the	Yu et al, 2016

		five behavioral domains (gross motor, fine motor, language, adaptive, and personal–social behaviors)	interaction between cord serum Mn and BDNF was significant ($p < 0.001$). The authors conclude that elevated prenatal Mn exposure was associated with impaired neurodevelopment which may be mediated by BDNF	
Cord blood Mn	933 mother-new-born pairs; Shanghai, China	Neonatal behavioural neurological assessments (NBNA); 5 sections to assess behaviour, active tone, passive tone, primary reflexes and general assessment	The median serum Mn concentration was 4.0 µg/L. After adjusting for potential confounders, a high level of Mn (>/=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 Mn and NBNA after adjusting for potential confounders. NBNA score decreased with increasing Mn levels after 5.0 µg/L(LgMn>/=0.7). Cord serum Mn >/=5.0 µg/L had adverse effects on behaviour, active tone and general reactions (p<0.001)	Yu et al, 2014
Blood lead and Mn	455 children from above study		Mean (SD) blood concentrations at 12 and 24 months were 24.7 (5.9) µg/L and 21.5 (7.4) µg/L for Mn 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 highest Mn exposures. A significant Mn–lead interaction was observed only at 18 months for children in the highest quintile of 12-month blood Mn [β = –1.74 (95% CI: –3.00, –0.49)] ($p < 0.05$). 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 Mn levels, compared with 1.80 points (i.e., –0.05 + –0.01 + –	Claus Henn et al, 2012

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