

Manganese: summary of epidemiologic evidence

February 28, 2005

1. Overall summary

This section summarizes epidemiologic evidence cited in the tables below and will be updated as new evidence becomes available. I would appreciate feedback on any errors or omissions.

Health effect	Level of evidence ^a	Comments
Fetal death	Maternal prenatal exposure (Inadequate)	A case-control study of late fetal deaths (stillbirths) in Massachusetts found no association with drinking water manganese levels in the communities of maternal residence (Aschengrau et al 1993).
Birth defects	Maternal prenatal exposure (Inadequate)	A very small case-control study in India found no association between congenital hydrocephalus or meningomyelocele and breast milk manganese levels (Dang et al 1983). Another very small case-control study in Turkey found an <i>inverse</i> association between birth defects (any type) and infant and maternal hair manganese levels (Saner et al 1985). A case-control study of birth defects (any type) in Massachusetts found no association with drinking water manganese levels in the communities of maternal residence (Aschengrau et al 1993). A literature review concluded that there is inadequate evidence for an association between birth defects and prenatal manganese exposure in humans; studies in experimental animals found increased risk of skeletal abnormalities (Agency for Toxic Substances and Disease Registry 2000).
Birth weight	Maternal prenatal exposure (Inadequate)	A small Swedish birth cohort study showed no association between birth weight adjusted for gestation length and placental manganese levels (Osman et al 2000).
Neurologic abnormalities: children	High-level childhood exposure Sufficient	Case reports indicate that children exposed to high levels of manganese from parenteral nutrition developed neurologic abnormalities including mild psychomotor retardation, hyperactivity and frequent static and intention tremor and MRI abnormalities (Fell et al 1996, Komaki et al 1999). The latter report indicated that symptoms and MRI abnormalities disappeared after manganese administration ceased (Komaki et al 1999). A literature review concluded that children exposed to high manganese levels because of liver disease with impaired excretion or dependency on parenteral nutrition developed neurotoxicity including loss of motor control of limbs and tremor (Agency for Toxic Substances and Disease Registry 2000). Investigation of a child age 10 years exposed to drinking water with a high manganese level (1.2 mg/L) found normal cognitive function but did find teacher-reported inattentiveness and markedly low scores on verbal and visual memory tests (Woolf et al 2002).

	Low-level childhood exposure (Inadequate)	A small cross-sectional study of Chinese children age 11-13 years showed that children living in a region with drinking water manganese levels of 240-350 µg/L had significantly lower neuropsychologic scores (manual dexterity, digit span, digit symbol, Benton visual retention and pursuit aiming tests) than those in a comparison region with levels of 30-40 µg/L; most test scores were inversely associated with current hair manganese levels (He et al 1994). The latter study also found that serum neurotransmitter levels (5-hydroxytryptamine, dopamine, norepinephrine, acetylcholine esterase) were lower among children in the contaminated area and that teacher-rated Chinese language and mathematic scores were inversely associated with serum neurotransmitter levels (Zhang et al 1995).
Hyperactivity	Low-level childhood exposure (Inadequate)	Two small case-control studies of hyperactive children found a borderline (Barlow 1983) or significant (Collipp et al 1983) association with current hair manganese levels. There appear to have been no subsequent reports of epidemiologic studies on this relationship.
Convulsive disorders	Childhood exposure (Inadequate)	A small hospital-based case-control study in Toronto found an <i>inverse</i> association between childhood convulsive disorders and current blood manganese level (Dupont and Tanaka 1985). A case report from Japan noted seizures in a girl age 2 years who had an elevated blood manganese level (9.7 µg/dL) from parenteral nutrition (Komaki et al 1999).
Neuropsychologic function	Prenatal maternal exposure (Inadequate)	A birth cohort study in France found no association between cognitive function scores at ages 9 months and 3 and 6 years and maternal and cord blood, hair or placental manganese levels (Takser et al 2003). Attention, non-verbal memory and hand skill scores at age 3 years were inversely associated with cord blood but not the other manganese exposure indices.
Neurologic abnormalities: adults	High-level environmental exposure (mainly ingestion) Sufficient	An expert panel concluded that residents of Guam developed Parkinson's disease, amyotrophic lateral sclerosis and dementia decades after their exposure to environmental manganese, iron and aluminum ceased (Gorrell et al 1996). A report of a case series of adults in Groote Eylandt, Australia with a syndrome similar to amyotrophic lateral sclerosis noted that 13 of 16 cases developed symptoms during childhood or adolescence and had a history of living in a region with high soil manganese levels (Kilburn 1987). Although interesting, no firm conclusions can be drawn from this case-only study.
	Low-level environmental exposure (mainly ingestion) (Inadequate)	A small cross-sectional study of adults in Greece found an association between neurologic assessment scores for symptoms and signs of Parkinson's disease and drinking water manganese levels; the study subjects' hair but not blood manganese levels were associated with drinking water manganese levels (Kondakis et al 1989). A very small cross-sectional study in Germany found no association between neurologic assessment scores for symptoms and signs of Parkinson's disease and drinking water or blood manganese levels (Vieregge et al 1995). Both studies found no association between blood manganese and drinking water manganese levels. A cross-sectional study of persons living near a former manganese alloy

	Occupational exposure (mainly inhalation) Sufficient	<p>plant in Canada found an association between slower arm movements and learning and memory deficits and blood manganese in men but not women (Mergler et al 1999). Two reviews concluded that there is limited epidemiologic evidence that chronic environmental exposure to manganese may cause neurotoxicity similar to Parkinson's disease (Mergler 1999, Hudnell 1999). There have been no studies of the possible role of childhood environmental manganese exposure and risk of Parkinson's disease.</p> <p>Several literature reviews concluded that occupational exposure to relatively high levels of airborne manganese can cause severe neurotoxicity similar to Parkinson's disease with disease progression after exposure ceases (Mergler and Baldwin 1997, Davis 1998, 1999, Mergler 1999, Agency for Toxic Substances and Disease Registry 2000).</p>
Neurotoxicity: general considerations		<p>Davis (1998) noted that children may be at risk during critical developmental stages and that neonatal exposure of experimental animals causes reduced brain dopamine levels and neurotoxicity with primates being more susceptible than rodents, especially with regard to behavioural and motor effects. A review of animal studies concluded that manganese at low oral doses is an essential trace dietary element but it is a cumulative neurotoxicant with toxicity varying by exposure route, dose and dose rate; it also noted that refined experimental methods including neurochemistry and highly structured observations have shown low-dose neurotoxic effects in animals (Newland 1999). A review of manganese toxicity concluded that deficient or excess manganese uptake in brain tissue can cause neurotoxic effects (Aschner 2000). An experimental study of rats given dietary manganese supplements during postnatal days 1-20 found dose-response relationships for passive avoidance errors at postnatal days 32 and 64 (Tran et al 2002a, 2002b). The latter study also found an inverse relationship between brain striatal dopamine concentration and manganese dose.</p>
Male fertility	Occupational exposure (Inadequate)	<p>Two small cohort studies found reduced male fertility among men occupationally exposed to airborne manganese, compared to men in other occupations (Lauwerys et al 1985, Gennart et al 1992). The latter study found no association between fertility and recent exposure. A cohort study of metal workers and welders in the Netherlands found a reduced likelihood of conception among welders (welders are exposed to manganese and other metals and toxicants) who smoked but not among non-smokers (Hjollund et al 1998).</p>
Semen quality	Environmental exposure (Inadequate)	<p>A case-control study showed no association between semen quality and urinary manganese levels (Tielemans et al 1999).</p>
Childhood diabetes	Environmental exposure (Inadequate)	<p>An ecologic study in England found no association between type I diabetes among children age 0-15 years and current community drinking water manganese levels (Zhao et al 2001).</p>

^a Sufficient evidence: based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed.

Limited evidence: relationships for which several epidemiologic studies, including at least one case-control or cohort study, showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders.

Inadequate evidence: relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or showed little or no evidence of exposure-risk relationships.

Levels in parentheses are the author's interpretation of available evidence.

2. Developmental effects

Reference, location	Design	Exposure	Results	Association	Covariates
(Dang et al. 1983), India	Case-control study, 9 infants with congenital hydrocephalus or meningomyelocele, 16 normal infants	Measured mother's breast milk manganese, molybdenum, arsenic, zinc, copper	Hydrocephalus or meningomyelocele not associated with breast milk manganese level	25 vs 23 $\mu\text{g/g}$	
(Saner et al. 1985), Turkey	Case-control study, 18 preterm infants, 12 infants with birth defects, 31 full-term healthy infants; measured maternal and infant hair manganese levels	Mean hair manganese levels were 2.4-2.5 $\mu\text{g/g}$ for mothers of full-term and preterm infants and 0.6 $\mu\text{g/g}$ for mothers of infants with birth defects	Birth defects associated with lower infant and maternal hair manganese levels	$t=3.4$ ($p < 0.001$)	
(Aschengrau et al. 1993), Massachusetts	Case-control study nested within cohort of 14,130 women enrolled at delivery with gestation at least 20 wk, 1977-1980; included 1,039 birth defects, 77 stillbirths, 1,177 controls	Assessed drinking water quality in 155 communities where women lived during pregnancy	Stillbirths not associated with drinking water manganese levels (crude odds ratio, manganese ≥ 20 vs < 20 $\mu\text{g/L}$)	0.8	
			Major birth defects not associated with drinking water manganese levels (crude odds ratio, manganese ≥ 20 vs < 20 $\mu\text{g/L}$)	1.1	
(Osman et al. 2000), Sweden	Birth cohort study, 106 mother-infant pairs, 17 spontaneous abortions	Measured placental manganese, cadmium, lead, and several essential elements and maternal and cord blood cadmium, lead, zinc, and selenium levels	No association between weight, length and head circumference and placental manganese levels		Maternal age, parity, smoking, gestation length, gender, cord blood cadmium, lead, zinc, selenium
(Agency for Toxic Substances and Disease Registry,	Literature review		Limited evidence for association between skeletal abnormalities and high prenatal		

Reference, location	Design	Exposure	Results	Association	Covariates
2000), USA			manganese exposure in experimental animals		

Developmental effects: summary

Fetal death

A case-control study of late fetal deaths (stillbirths) in Massachusetts found no association with drinking water manganese levels in the communities of maternal residence (Aschengrau et al 1993).

Birth defects

A very small case-control study in India found no association between congenital hydrocephalus or meningomyelocele and breast milk manganese levels (Dang et al 1983). Another very small case-control study in Turkey found an *inverse* association between birth defects (any type) and infant and maternal hair manganese levels (Saner et al 1985). A case-control study of birth defects (any type) in Massachusetts found no association with drinking water manganese levels in the communities of maternal residence (Aschengrau et al 1993). A literature review concluded that there is inadequate evidence for an association between birth defects and prenatal manganese exposure in humans; studies in experimental animals found increased risk of skeletal abnormalities (Agency for Toxic Substances and Disease Registry 2000).

Birth weight

A small Swedish birth cohort study showed no association between birth weight adjusted for gestation length and placental manganese levels (Osman et al 2000).

3. Neurotoxic effects

Reference, location	Design	Exposure	Results	Association ^a	Covariates
(Barlow 1983), United Kingdom	Case-control study, 68 hyperactive children, 71 controls, age < 16 yr (note: controls had higher SES than cases)	Measured hair manganese, cadmium, copper, iron, lead, zinc, magnesium, calcium and aluminum levels	Borderline association between hyperactivity and hair manganese (mean level, cases vs controls)	0.84 vs 0.68 $\mu\text{g/g}$ (p= 0.10)	
(Collipp et al. 1983), USA	Hospital-based case-control study, 16 hyperactive children with learning disability, 44 controls, age 7-10 yr; conducted neuropsychologic tests and evaluated speech, language and hearing and assessed infant feeding practices; also measured hair manganese levels in 70 infants and children	Measured hair manganese; levels increased with duration of formula feeding from 0.2 $\mu\text{g/g}$ at birth to 1.0 $\mu\text{g/g}$ at age 6 wk and 0.7 $\mu\text{g/g}$ at age 4 mos (compared to 0.3 $\mu\text{g/g}$ at age 4 mos in breast-fed infants)	Hyperactivity with learning disability associated with hair manganese level (cases vs controls)	0.43 vs 0.27 $\mu\text{g/g}$ (p < 0.05)	
(Dupont and Tanaka 1985), Canada	Hospital-based case-control study, 197 children with convulsive disorders, 120 controls, age 0-18 yr	Mean blood manganese in controls varied by age from 1.4 to 1.7 $\mu\text{g/dL}$	Association between convulsive disorder and lower blood manganese level	+	
(Kilburn 1987), Groote Eylandt Island, Australia	Case series, 16 persons with neurologic syndrome of amyotrophy, weakness and distal limb muscle wasting	High soil manganese levels	13/16 cases onset during childhood or adolescence; apparent association with manganese exposure but no controls or comparison groups		
(Kondakis et al. 1989), Greece	Cross-sectional study, 188 persons age 50+ yr, living in 3 regions of Greece with varying drinking water manganese concentrations; neurologic examination for signs of Parkinson's disease	Drinking water manganese levels in the 3 regions were 3.6-15, 82-253 and 1800-2300 $\mu\text{g/L}$; blood manganese levels in low and high exposure regions were	Association between neurologic symptom scores and residence in regions with higher drinking water manganese levels (did not report data for relationship between neurologic scores and blood or	2.7 vs 3.9 vs 5.2 (p < 0.001)	The 3 regions were similar with regard to occupation (mainly agricultural workers), education

Reference, location	Design	Exposure	Results	Association ^a	Covariates
		15.8 and 16.5 µg/L; hair manganese levels in low, intermediate and high exposure regions were 3.5, 4.5 and 11 µg/g	hair manganese levels); neurologic symptom scores in low, intermediate and high drinking water manganese regions		
(He et al. 1994), China	Cross-sectional study, 92 matched-pairs of children age 11-13 yr from an area using high-manganese sewage irrigation and a control area; assessed neuropsychologic function by conducting digit span, Santa Ana manual dexterity, digit symbol, Benton visual retention test and pursuit aiming tests	Drinking water in exposed and control regions, respectively, contained manganese levels of 0.24-0.35 mg/L and 0.03-0.04 mg/L; hair manganese levels in exposed and control regions, respectively, were 1.25 µg/g and 0.96 µg/g	Neuropsychologic scores were significantly lower among children in the exposed compared to those in the control region	+	
			Scores on most neuropsychologic tests inversely associated with hair manganese levels		
(Zhang et al. 1995), China	Cross-sectional study (as above); measured serum 5-hydroxytryptamine (5-HT), dopamine, norepinephrine and acetylcholine esterase	Average hair and blood manganese levels in exposed regions were 1.2 µg/g and 34 µg/L	School performance inversely associated with serum neurotransmitter levels; the latter were inversely associated with residence in the contaminated area		
(Vieregge et al. 1995), Germany	Cross-sectional study, 41 adults chronically exposed to well water containing high manganese levels, 74 adults chronically exposed to well water with low manganese levels; assessed neurologic signs of Parkinson's disease (esp. fine motor ability)	Drinking water manganese levels were ≥ 300 µg/L (range 300-2160 µg/L) or < 50 µg/L; mean blood manganese in high and low exposure groups were 8.5 and 7.7 µg/L	No association between neurologic test scores and drinking water or blood manganese levels		Groups similar with respect of age, sex, nutritional habits, drug intake

Reference, location	Design	Exposure	Results	Association ^a	Covariates
(Fell et al. 1996), UK	Case series, 11 children age 0.5-17 mos, received parenteral nutrition for at least 2 wk; conducted neurologic examinations and MRI scans at baseline and 4 and 8 mos later	Given manganese at levels of 44-55 $\mu\text{g}/\text{kg}/\text{day}$; median blood manganese 71.5 (range 33.8-101 $\mu\text{g}/\text{L}$)	The 2 children with highest manganese levels had dystonic limb movements and abnormal posturing; also had bilateral, symmetrical, abnormal MRI signals from globus pallidus and subthalamic nuclei		
(Gorrell et al. 1996), USA	Summary of expert conference on the role of environmental factors in Parkinson's disease (PD)		PD, amyotrophic lateral sclerosis and dementia can develop decades after exposure to high environmental manganese, iron and aluminum ceases (based on follow-up of Guamanians)		
(Mergler and Baldwin 1997), Canada	Review of literature on early manifestations of manganese neurotoxicity in humans		Early signs of manganese neurotoxicity include slowed motor functions, tremor, reduced response speed, enhanced sense of smell, mood change and memory and intellectual deficits		
			Manganese-induced neurotoxicity progresses after exposure ceases		
(Davis 1998; Davis 1999), USA	EPA review of potential health risks of MMT/inhaled manganese		Low-level occupational exposure to airborne manganese causes neurotoxic deficits including the speed and coordination of motor function		
			Children may be at risk during critical developmental stages;		

Reference, location	Design	Exposure	Results	Association ^a	Covariates
			neonatal exposure of experimental animals causes reduced brain dopamine levels and neurotoxicity – primates appear to be more susceptible to neurotoxic effects of manganese than rodents, especially behavioural and motor effects		
			Older persons may be at risk because of cumulative exposure and loss of neurons attributable to manganese		
(Hudnell 1999), USA	Review of literature on health effects of environmental (non-occupational) manganese exposure		Chronic exposure to manganese in water or air may cause adverse health effects in humans including extrapyramidal, neuromotor dysfunctions similar to Parkinson's disease, cognitive deficits and altered mood		
			Limited evidence for an association between Parkinson-like syndrome and blood manganese in the 7.5-25 µg/L range		
(Newland 1999), USA	Review of animal studies of manganese neurotoxicity		At low oral doses, manganese is an essential trace dietary element; however, it is a cumulative neurotoxicant with toxicity varying by exposure route, dose and dose rate		

Reference, location	Design	Exposure	Results	Association ^a	Covariates
			Refined experimental methods including neurochemical outcomes and highly structured observations have shown low-dose neurotoxic effects in animals		
(Mergler 1999), Canada	Review of literature on neurotoxic effects of low-level environmental manganese exposure		High occupational exposure to inhaled manganese can cause severe neurotoxicity similar to Parkinson's disease; disease can progress after exposure ceases		
			Limited epidemiologic evidence for associations between environmental manganese exposure and neurotoxic effects		
(Komaki et al. 1999), Japan	Case report, tremor and seizures in a girl age 2 yr receiving total parenteral nutrition; conducted neurologic examination and MRI scans	Elevated blood manganese (9.7 µg/dL)	MRI showed symmetrical bilateral hyperintensity in the basal ganglia, brainstem and cerebellar white matter; neurologic examination showed mild psychomotor retardation, hyperactivity and frequent static and intention tremor		
(Mergler et al. 1999), Canada	Cross-sectional study, 273 persons living near a former manganese alloy plant but not occupationally exposed, age 20-69 yr; assessed mood and symptoms and conducted a neurologic examination and several tests of motor, sensory and	Measured blood manganese (median 7.3, range 2.5-16 µg/L), lead and mercury and serum iron	Coordinated upper limb movement performance inversely related to blood manganese	++	Age, sex, education, smoking, alcohol, blood lead and mercury, serum iron, fish consumption from

Reference, location	Design	Exposure	Results	Association ^a	Covariates
	cognitive function including coordinated upper limb movements, learning, memory, smell, visual acuity and contrast sensitivity				Upper St. Lawrence River
			Symptoms and MRI abnormalities disappeared after manganese administration ceased		
			Association between slower arm movements in men but not women	(+)	
			Association between learning and memory deficits and blood manganese in men and women	+	
(Agency for Toxic Substances and Disease Registry, 2000), USA	Literature review		Children exposed to high manganese levels because of liver disease with impaired excretion or dependency on parenteral nutrition developed neurotoxicity including loss of motor control of limbs and tremor		
			Occupational exposure to high levels of airborne manganese can cause severe neurotoxicity including permanent neurologic effects and mood swings		
(Aschner 2000), USA	Review of literature on manganese transport into brain		Deficient or excess manganese in brain tissue can cause neurotoxic effects		
(Woolf et al.	Case report, child age 10 yr,	Exposed for 5 yr to well	Teacher-reported inattentiveness,		

Reference, location	Design	Exposure	Results	Association ^a	Covariates
2002), USA	exposed for 5 yr to well water containing high manganese levels; assessed school performance and conducted neuropsychologic tests	water containing manganese (1.2 mg/L); blood manganese was 38 µg/L, hair manganese was 3.1 µg/g	normal cognitive function, markedly low scores on verbal and visual memory tests		
(Tran et al. 2002a; Tran et al. 2002b) USA	Randomized exposure of neonatal rats to supplemental dietary manganese; assessed tissue manganese accumulation, brain dopamine levels and neurodevelopmental status and behaviour	Neonatal rats were fed diets supplemented with 0, 50, 250 or 500 µg/day during postnatal days 1-20	Dose-response relationship between passive avoidance errors at postnatal day 32 and manganese dose	+	
			Dose-response relationship between burrowing detour and passive avoidance errors during postnatal days 50-64 and manganese dose	+	
			Inverse relationship between brain striatal dopamine concentration and manganese dose		
(Takser et al. 2003), France	Birth cohort study, 247 mother-infant pairs; conducted neuropsychologic examinations at ages 9 mos (Brunet-Lezine developmental quotient) and 3 and 6 yr (McCarthy general cognitive index)	Measured manganese in maternal and cord blood, hair and placenta samples	Brunet-Lezine developmental quotient at age 9 mos and McCarthy CGI scores at ages 3 and 6 years not associated with manganese exposure indices at birth (result stated without supporting data)		Maternal and cord blood lead, maternal age, education, duration of labour, child sex, gestation length, birth weight, prenatal tea, coffee, alcohol, smoking
			Attention, non-verbal memory and hand skill scores at age 3 yr inversely associated with cord	attention β=-0.03, p=0.01	As above

Reference, location	Design	Exposure	Results	Association ^a	Covariates
			blood but not maternal blood, hair or placental manganese levels; β -coefficients for cord blood	non-verbal memory $\beta=-0.02$, $p=0.05$ hand skill $\beta=-0.03$, $p=0.01$	
			McCarthy subscale scores at age 6 yr not associated with any manganese exposure index at birth		

Neurotoxic effects: summary

Children

Neurologic abnormalities

High-level exposure Case reports indicate that children exposed to high levels of manganese from parenteral nutrition developed neurologic abnormalities including mild psychomotor retardation, hyperactivity and frequent static and intention tremor and MRI abnormalities (Fell et al 1996, Komaki et al 1999). The latter report indicated that symptoms and MRI abnormalities disappeared after manganese administration ceased (Komaki et al 1999). A literature review concluded that children exposed to high manganese levels because of liver disease with impaired excretion or dependency on parenteral nutrition developed neurotoxicity including loss of motor control of limbs and tremor (Agency for Toxic Substances and Disease Registry 2000). Investigation of a child age 10 years exposed to drinking water with a high manganese level (1.2 mg/L) found normal cognitive function but teacher-reported inattentiveness and markedly low scores on verbal and visual memory tests (Woolf et al 2002).

Low-level exposure A small cross-sectional study of Chinese children age 11-13 years showed that children living in a region with drinking water manganese levels of 240-350 $\mu\text{g/L}$ had significantly lower neuropsychologic scores (manual dexterity, digit span, digit symbol, Benton visual retention and pursuit aiming tests) than those in a comparison region with levels of 30-40 $\mu\text{g/L}$; most test scores were inversely associated with current hair manganese levels (He et al 1994). The latter study also found that serum neurotransmitter levels (5-hydroxytryptamine, dopamine, norepinephrine, acetylcholine esterase) were lower among children in the contaminated area and that teacher-rated Chinese language and mathematic scores were inversely associated with serum neurotransmitter levels (Zhang et al 1995).

Hyperactivity

Two small case-control studies of hyperactive children found a borderline (Barlow 1983) or significant (Collipp et al 1983) association with current hair manganese levels. There appear to have been no subsequent reports of epidemiologic studies on this relationship.

Convulsive disorders

A small hospital-based case-control study in Toronto found an *inverse* association between childhood convulsive disorders and current blood manganese level (Dupont and Tanaka 1985). A case report from Japan noted seizures in a girl age 2 years who had an elevated blood manganese level (9.7 µg/dL) from parenteral nutrition (Komaki et al 1999).

Neuropsychologic function

A birth cohort study in France found no association between cognitive function scores at ages 9 months and 3 and 6 years and maternal and cord blood, hair or placental manganese levels (Takser et al 2003). The latter study found that attention, non-verbal memory and hand skill scores at age 3 years were inversely associated with cord blood but not the other manganese exposure indices.

Adults*Neurologic abnormalities*

High-level environmental exposure (mainly ingestion) An expert panel concluded that residents of Guam developed Parkinson's disease, amyotrophic lateral sclerosis and dementia decades after their exposure to environmental manganese, iron and aluminum ceased (Gorrell et al 1996). A report of a case series of adults in Groote Eylandt, Australia with a syndrome similar to amyotrophic lateral sclerosis noted that 13 of 16 cases developed symptoms during childhood or adolescence and had a history of living in a region with high soil manganese levels (Kilburn 1987). Although interesting, no firm conclusions can be drawn from this case-only study.

Low-level environmental exposure (mainly ingestion) A small cross-sectional study of adults in Greece found an association between neurologic assessment scores for symptoms and signs of Parkinson's disease and drinking water manganese levels; the study subjects' hair but not blood manganese levels were associated with drinking water manganese levels (Kondakis et al 1989). A very small cross-sectional study in Germany found no association between neurologic assessment scores for symptoms and signs of Parkinson's disease and drinking water or blood manganese levels (Viergge et al 1995). Both studies found no association between blood manganese and drinking water manganese levels. Davis (1998) noted that children may be at risk during critical developmental stages and that neonatal exposure of experimental animals causes reduced brain dopamine levels and neurotoxicity with primates being more susceptible than rodents, especially with regard to behavioural and motor effects. A cross-sectional study of persons living near a former manganese alloy plant in Canada found an association between slower arm movements and learning and memory deficits and blood manganese in men but not women (Mergler et al 1999). Two reviews concluded that there is limited epidemiologic evidence that chronic environmental exposure to manganese may cause neurotoxicity similar to Parkinson's disease (Mergler 1999, Hudnell 1999). There have been no studies of the possible role of childhood environmental manganese exposure and risk of Parkinson's disease.

Occupational exposure (mainly inhalation) Several literature reviews concluded that occupational exposure to relatively high levels of airborne manganese can cause severe neurotoxicity similar to Parkinson's disease with disease progression after exposure ceases (Mergler and Baldwin 1997, Davis 1998, 1999, Mergler 1999, Agency for Toxic Substances and Disease Registry 2000).

General considerations

A review of animal studies concluded that manganese at low oral doses is an essential trace dietary element but it is a cumulative neurotoxicant with toxicity varying by exposure route, dose and dose rate; it also noted that refined experimental methods including neurochemistry and highly structured observations have shown low-dose neurotoxic effects in animals (Newland 1999). A review of manganese toxicity concluded that deficient or excess manganese uptake in brain tissue can cause neurotoxic effects (Aschner 2000). An experimental study of rats given dietary manganese supplements during postnatal days 1-20 found dose-response relationships for passive avoidance errors at postnatal days 32 and 64 (Tran et al 2002a, 2002b). The latter study also found an inverse relationship between brain striatal dopamine concentration and manganese dose.

4. Reproductive health

Reference, location	Design	Exposure	Results	Association ^a	Covariates
(Lauwerys et al. 1985), Belgium	Cohort study, 85 workers exposed to airborne manganese salts, 103 workers exposed to airborne elemental mercury, 182 men in comparison groups, age 16-45 yr; assessed fertility of exposed men before and after exposure; expected number of children based on fertility of comparison group	Median airborne manganese level 0.97 (range 0.07-8.6 mg/m ³); average blood manganese level among exposed men was 1.3 (range 0.1-3.3 µg/dL); corresponding mean urinary manganese level was 4.4 (range 0.1-141) µg/g creatinine	Fertility lower in group exposed to manganese (observed vs expected number of children)	39 vs 70.5 (p < 0.05)	Groups similar with regard to age, age of wives, duration of employment, smoking, alcohol, education, wife's occupation
(Gennart et al. 1992), Belgium	Cohort study, 74 lead battery plant workers, 83 cadmium smelter workers, 70 alkaline battery plant workers exposed to airborne manganese dust, 138 unexposed workers (polyethylene plant, battery container producing plant, smelter maintenance workers); self-reported reproductive history	Measured blood lead and manganese and urinary cadmium and manganese	Birth rate decreased among manganese-exposed alkaline battery workers (relative risk of live birth, post- vs pre-exposure periods)	0.7 (CI 0.5-0.9)	Age
			Likelihood of a live birth not reduced during manganese exposure period (odds ratio, post- vs pre-employment period)	1.0 (CI 0.7-1.6)	
			Likelihood of a live birth not increased during years when airborne manganese levels below group median level	0.8 (CI 0.5-1.4)	
(Hjollund et al. 1998),	Cohort study, 430 couples including 201 male metal workers and 130	Self-reported occupational exposures at baseline and any	Likelihood of conception reduced among welders	smokers 0.4 (0.2-1.0)	

Reference, location	Design	Exposure	Results	Association ^a	Covariates
Denmark	male welders, recruited 1992-1994; followed for 6 menstrual cycles after discontinuing birth control	changes solicited by monthly follow-up questionnaires	who smoked but not among non-smokers; fecundability ratios, welders vs metal workers	non-smokers 1.2 (0.7-1.9)	
(Tielemans et al. 1999), The Netherlands	Case-control study, based on infertility clinics; 3 case definitions: (A) 692 with sperm concentration < 20x10 ⁶ /ml or < 50% motile or < 14% normal morphology, (B) sperm concentration < 5x10 ⁶ /ml or < 10% motile or < 5% normal morphology, (C) azoospermia (no sperm)	Self-reported occupational history, job-exposure matrix; urine from 69 cases and 20 controls tested for nickel, chromium, cadmium and manganese	No association between semen quality and urinary manganese (mean urinary manganese levels in cases and controls); also no associations with urinary cadmium, chromium or nickel	0.52 vs 0.56 µg/g creatinine (p = 0.68)	

Reproductive health: summary

Male fertility

Two small cohort studies found reduced male fertility among men occupationally exposed to airborne manganese, compared to men in other occupations (Lauwerys et al 1985, Gennart et al 1992). The latter study found no association between fertility and recent exposure.

Semen quality

A case-control study showed no association between semen quality and urinary manganese levels (Tielemans et al 1999).

5. Diabetes Reference, location	Design	Exposure	Results	Association ^a	Covariates
(Zhao et al. 2001), England	Ecologic study, 517 children age 0-15 yr with type I diabetes living in 40 drinking water supply regions	Measured manganese (median 10, range 1-440 µg/L), copper, aluminum, calcium, iron, nitrate, zinc, and magnesium in drinking water	No association between childhood type I diabetes and drinking water manganese levels	SIR=1.0	

Diabetes: summary

An ecologic study in England found no association between type I diabetes among children age 0-15 years and current community drinking water manganese levels (Zhao et al 2001).

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