

Mercury: summary of epidemiologic evidence

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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. don.wigle@sympatico.ca

Health effect	Level of evidence ^a	Comments
Fetal death	(Inadequate)	Case-control studies in Massachusetts found a borderline association between early fetal deaths (spontaneous abortions) (Aschengrau et al 1989) but not late fetal deaths (stillbirths) (Aschengrau et al 1993) and detectable mercury levels in drinking water in the community of maternal residence. A small birth cohort study in North Carolina found no excess fetal deaths (Elghany et al 1997). An expert panel concluded that prenatal methylmercury exposure causes fetotoxicity in mice (World Health Organization 1990).
Birth weight (unadjusted for gestation length)	(Inadequate)	A birth cohort study in the Faroe Islands found a borderline <i>positive</i> association between birth weight and cord blood mercury levels among non-smoking women (Grandjean and Weihe 1993). A small birth cohort study in Peru found no association between birth weight and prenatal maternal hair mercury levels (Marsh et al 1995). A retrospective cohort study in Greenland found a borderline inverse association between birth weight and prenatal maternal blood mercury levels (Bjerregaard and Hansen 1996).
Birth weight adjusted for gestation length	(Inadequate)	A German birth cohort study found an association between small for gestational age infants and maternal prenatal occupation exposure to mercury or mercury compounds (Seidler et al 1999). A small birth cohort study in the Faroe Islands found no association between birth weight adjusted for gestation length and cord blood mercury levels among singleton spontaneous live births (Grandjean et al 2001c).
Gestation length	(Inadequate)	A small birth cohort study in the Faroe Islands found no association between gestation length and cord blood mercury levels among singleton spontaneous live births (Grandjean et al 2001c).
Total birth defects	(Inadequate)	A large case-control study in Massachusetts found no association between total birth defects and drinking water mercury levels in the community of maternal residence (Aschengrau et al 1993). A retrospective birth cohort study found no increased risk of birth defects among infants of women living near a copper smelter in Sweden that emitted mercury and other toxicants (Wulff et al 1996). A small birth cohort study in North Carolina found a statistically non-significant excess of birth defects among women occupationally exposed to airborne elemental mercury (Elghany et al 1997). An expert panel concluded that prenatal methylmercury exposure causes birth defects in rats (World Health Organization

		1990).
Specific birth defects	(Inadequate)	A large case-control study of anencephaly (a neural tube birth defect) in Canada found no association with drinking water mercury levels in the community of maternal residence (Elwood and Coldman 1981). A case-control study of cardiac birth defects in Massachusetts found a borderline association between patent ductus arteriosus and drinking water mercury levels in the community of maternal residence (Zierler et al 1988).
Postnatal growth	(Inadequate)	A small birth cohort study in the Faroe Islands found inverse associations between height and weight at ages 18 and 42 months and cord blood mercury levels, independent of duration of breastfeeding (Grandjean et al 2003b).
Delayed milestones (age at first sitting, standing, walking, talking)	High-dose prenatal methylmercury exposure Sufficient High-level postnatal methylmercury exposure (Inadequate) Low-level prenatal methylmercury exposure Limited	<p>A review of congenital methylmercury poisoning at Minamata noted that most infants age 1-2 years could not sit or walk alone or talk, had abnormal reflexes, increased muscle tone and excessive salivation and displayed involuntary movements (Harada 1977). This study also found that none of the exposed children could understand maternal speech and most could not walk at age 3 years; only half could walk alone at age 9-14 years and all had speech impairment. Among children prenatally exposed to high doses of methylmercury in Iraq, delayed developmental milestones were associated with prenatal maternal hair mercury levels (Marsh et al 1980, 1981, 1987). An expert group convened by the World Health Organization (1990) concluded that extrapolation of Iraqi data suggest increased risk of delayed developmental milestones at prenatal maternal hair mercury levels as low as 10-20 µg/g, a view shared by recent literature reviews (Clarkson 1997, 2002, Newland 2002).</p> <p>Among postnatally exposed Iraqi infants, there was a statistically non-significant association between delayed milestones (ages at sitting, standing, walking) and lactational and/or dietary methylmercury exposure before age 10 months, compared to those exposed at older ages (Amin-Zaki et al 1981).</p> <p>A birth cohort study in the Faroe Islands found no associations between age at milestone development and prenatal maternal hair or cord blood mercury levels; moreover, <i>early</i> milestone development was associated with breastfeeding duration and infant hair mercury level at age 12 months (Grandjean et al 1995). A small birth cohort study in Peru found no associations between age at milestone development and prenatal maternal hair mercury levels (Marsh et al 1995). A birth cohort study in the Seychelles Islands found an association between age at walking and prenatal maternal hair mercury levels in boys but not girls; age at talking was not associated with prenatal maternal hair mercury (Myers et al 1997, Axtell et al 1998).</p>
Mental retardation,	High-level prenatal	An infant prenatally exposed to methylmercury because the mother and family consumed meat from a

cerebral palsy, seizures, deafness, blindness, dysarthria	methylmercury exposure Sufficient	pig fed methylmercury-treated seed grain had gross tremors of extremities at birth, irritability and increased muscle tone at postnatal week 6, grossly abnormal EEG at age 3 months and generalized myoclonic jerks at age 6 months; three older siblings developed ataxia, agitation, visual impairment and impaired consciousness but the mother had no symptoms (Snyder 1971). During the 1972 Iraq methylmercury poisoning episode, prenatally exposed infants had microcephaly and developed severe neurotoxicity including blindness, severely impaired hearing and generalized paralysis (Amin-Zaki et al 1974, 1979). Follow-up of prenatally exposed Iraqi infants found that cerebral palsy was associated with 3 rd trimester exposure (Amin-Zaki 1979). Delayed motor and speech development and seizures during infancy were associated with high prenatal maternal hair and postnatal blood mercury levels (Amin-Zaki 1981, Marsh et al 1980, 1981). There were dose-response relationships between abnormal neurologic signs and peak prenatal maternal hair mercury levels with stronger associations among boys than girls (Marsh et al 1987). An expert panel concluded that prenatal methylmercury exposure causes severe neurotoxicity among infants of women with hair mercury levels above 400 µg/g (World Health Organization 1990). This panel also concluded that methylmercury causes neurotoxic effects in all animal species studied with the fetus being more sensitive than adults. Prenatally exposed infants at Minamata appeared normal at birth but neurologic abnormalities started to appear at age 6 months and included primitive reflexes, cerebellar ataxia, strabismus, dysarthria, hyperkinesia, hypersalivation, spasticity (i.e., cerebral palsy-like syndrome) and seizures (Harada 1977, 1978, 1995, Watanabe and Satoh 1996). At age 1-7 years, children with Minamata disease all had impaired chewing/swallowing, speech, gait, coordination and mental development, inability to walk alone, increased muscle tone and incontinence; at age 9-14 years, all were mentally retarded (IQ<75) and still had muscle spasticity, ataxia and athetoid movements (Harada 1977). Although maternal and cord blood or hair samples were not collected in Minamata, a retrospective study of infants with severe neurotoxicity revealed elevated umbilical cord tissue mercury levels (Harada et al 1999). In both Iraq and Minamata, mothers of infants with congenital methylmercury poisoning generally had mild or no symptoms during pregnancy but some later developed one or more abnormalities including paresthesias, mild incoordination, constriction of visual fields, dysarthria and tremor (Harada 1978). Several literature reviews concluded that high-level prenatal methylmercury exposure causes severe neurotoxic effects in infants including mental retardation, cerebral palsy, seizures, deafness, blindness and dysarthria (Harada et al 1978, 1995, 1999, Myers and Davidson 1998, Myers et al 2000, Myers and Davidson 2000, National Academy of Sciences 2000, United Nations Environment Programme 2002, Clarkson 2002).
Ataxia, weakness and visual and other sensory deficits	High-level postnatal methylmercury exposure (Sufficient)	Children postnatally exposed to methylmercury from a pig fed methylmercury-treated seed grain developed ataxia, agitation, visual impairment and impaired consciousness but the mother had no symptoms (Snyder 1971). Two-year follow-up of 49 children exposed at age 0-14 years during the Iraq methylmercury poisoning episodes, found that the severity and persistence of ataxia, weakness and visual and sensory deficits were associated with baseline blood mercury levels (Amin-Zaki et al 1978).

		Children with mild/moderate poisoning improved slowly but all had persistent hyperreflexia; 5 of 17 blind children recovered partial sight and 7 of 18 children with severe poisoning had persistent physical and mental disability.
Abnormal muscle tone, deep tendon reflexes	Low-level prenatal methylmercury exposure (Inadequate)	A cross-sectional study of Aboriginal infants age 12-30 months in northern Quebec found that abnormal tendon reflexes in boys but not girls were associated with maximum prenatal maternal hair mercury levels but there was no dose-response relationship (McKeown-Eyssen et al 1983). A birth cohort study of almost 800 infants in the Seychelles Islands found no association between muscle tone, deep tendon reflexes and overall neurologic status and prenatal maternal hair mercury levels (Myers et al 1995b). A small birth cohort study in Peru also found no associations between deep tendon reflexes and prenatal maternal hair mercury levels (Marsh et al 1995). A small birth cohort study in the Faroe Islands found that a neurologic optimality score, but not the muscle tone component of the score, was inversely associated with cord blood mercury levels (Steuerwald et al 2000).
Cognitive function among preschool-age children	Low-level prenatal methylmercury exposure (Inadequate)	The Seychelles Islands birth cohort study found no associations between the Denver Developmental Screening Test scores, Bayley Scales of Infant Development or Fagan visual recognition and visual attention scores among infants age 6-29 months and prenatal maternal hair mercury levels (Myers et al 1995b, Davidson et al 1995). Using data from the latter study on Fagan tests of visual recognition memory and attention at age 6 months, the estimated average benchmark dose lower limit (BMDL) for a 10% probability of an adverse outcome was 26 µg/g for prenatal maternal hair (Crump et al 2000). A small birth cohort study among women who consumed Lake Ontario fish found no associations between Neonatal Behavioral Assessment Scale scores or Fagan Test of Infant Intelligence scores at ages 6 or 12 months and prenatal maternal hair mercury levels (Stewart et al 2000, Darvill et al 2000). A UK birth cohort study found no associations between MacArthur Communicative Development Inventory scores at age 15 months or Denver Developmental Screening Test scores at age 18 months and umbilical cord tissue mercury levels (Daniels et al 2004).
Cognitive function among school-age children	Low-level prenatal methylmercury exposure Limited	Literature reviews by Grandjean et al (1994, 1996) concluded that full-scale IQ deficits are associated with prenatal maternal hair mercury levels above 15 µg/g. In the Seychelles Islands pilot study, the McCarthy general cognitive index among children age 5 years was inversely associated with prenatal maternal hair mercury levels; after removal of outliers, these associations were not statistically significant (Myers et al 1995a). Follow-up of children in the latter study showed no associations between WISC-III subscale scores at age 9 years and prenatal maternal hair mercury levels (Davidson et al 2000). The Seychelles Islands birth cohort main study found no associations between full-scale IQ or subscale scores at ages 5 or 9 years and maternal or child hair mercury levels (Davidson et al 1998, Axtell et al 2000, Palumbo et al 2000, Myers et al 2003). Based on McCarthy general cognitive index values at age 5 years in the Seychelles Islands birth cohort study, the estimated benchmark dose lower

		<p>limit (BMDL) for a 10% probability of an adverse outcomes was 24 µg/g for prenatal maternal hair (Crump et al 2000). Results from generalized additive model analysis of the Seychelles Islands cohort data suggested a nonlinear dose-response relationship whereby McCarthy general cognitive index scores at age 5-6 years increased with prenatal maternal hair mercury concentrations up to 10 µg/g and then decreased (Axtell et al 2000). Literature reviews by Myers and colleagues concluded that there is limited evidence that low-level prenatal methylmercury exposure can cause developmental disabilities and no evidence that exposure to methylmercury from fish alone causes neurobehavioural deficits (Myers et al 2000a, Myers and Davidson 1998, 2000).</p> <p>In the Faroe Islands birth cohort study there were no associations between WISC similarity and block design subscale scores at age 7 years and prenatal maternal hair, cord blood or current child hair or blood mercury levels (Grandjean et al 1997, 1999b, 2001b). Reanalyses of the Faroe Islands birth cohort study showed that: (i) after excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, there were no associations between WISC subscale scores at age 7 years and cord blood mercury levels (Grandjean et al 2001a), and, (ii) restriction to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, there was a borderline inverse association between WISC block design scores at age 7 years and cord blood mercury levels (Grandjean et al 2003). A reanalysis of a New Zealand birth cohort study found a borderline inverse association between McCarthy general cognitive index scores at ages 6-7 years and prenatal maternal hair mercury levels (after excluding the child with the highest prenatal maternal hair mercury level) (Crump et al 1998).</p> <p>Expert panel reviews noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with language, verbal memory and other subtle neuropsychologic deficits in two large epidemiologic studies and experimental animal evidence for cognitive, motor and sensory deficits at low prenatal methylmercury exposure levels (National Academy of Sciences 2000, United Nations Environment Programme 2002). A recent literature review noted that among 46 neuropsychologic outcomes measured in the Seychelles Islands birth cohort study: (i) only one was unfavourably associated with prenatal methylmercury exposure, i.e., time to complete the grooved pegboard test using the non-preferred hand, boys age 9 years, and, (ii) there were two favourable associations with prenatal maternal hair mercury levels, i.e., language function at age 5 years and teacher-rated ADHD index at age 9 years (Davidson et al 2004). The latter review also noted that the Faroe Islands birth cohort study found associations between prenatal maternal hair and/or cord blood mercury levels and tests of memory, attention, language and visual spatial perception at age 7 years.</p>
Cognitive function among school-age children	Low-level postnatal methylmercury	A cross-sectional study of children age 5-7 years in the former East Germany found no association between WISC block design subtest scores and current urinary mercury levels (Walkowiak et al 1998).

	exposure indices (Inadequate)	A larger cross-sectional study of children age 7-12 years in the Amazon Basin found inverse associations between Stanford-Binet subscale scores for visuospatial/visuoconstructional and memory functions among children age 7-12 years and current child hair mercury levels (Grandjean et al 1999a).
Language	Low-level prenatal methylmercury exposure Limited	In the Seychelles Islands birth cohort study, language performance scores at ages 5-6 years were weakly and <i>positively</i> associated with prenatal maternal hair mercury levels (Davidson et al 1998). Results from generalized additive model analysis of the Seychelles Islands cohort data suggested a nonlinear dose-response relationship whereby language scores at age 5-6 years increased with prenatal maternal hair mercury concentrations up to 10 µg/g and then decreased (Axtell et al 2000). Using continuous values of language scores at age 5 years in the Seychelles Islands birth cohort study, the estimated benchmark dose lower limit (BMDL) for a 10% probability of an adverse outcomes was 25 µg/g for prenatal maternal hair mercury (Crump et al 2000). Language test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). In the Faroe Islands birth cohort study, language scores (Boston Naming Test) were inversely associated with prenatal maternal hair and cord blood mercury levels (Grandjean et al 1997, 1998, 1999b, 2001b). The association between language scores and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). However, the association was weaker and statistically non-significant after inclusion of umbilical cord tissue PCB levels in the analytic model (Grandjean et al 1997). Data from the Faroe Islands birth cohort study on language scores at age 7 years yielded a BMDL of 3.0 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found that language scores (Boston Naming Test) at age 7 years were inversely associated with cord blood mercury levels (Grandjean et al 2003). A literature review by the United Nations Environment Programme (2002) concluded that there is some evidence that low-level prenatal methylmercury exposure can cause language deficits. A UK birth cohort study showed that verbal comprehension scores at age 15 months and language test scores at age 18 months were not associated with umbilical cord tissue mercury levels but were favourably associated with maternal prenatal fish intake frequency (Daniels et al 2004).
	Low-level prenatal methylmercury exposure (Inadequate)	In the Seychelles Islands birth cohort study, language performance scores at ages 5-6 years were weakly and <i>positively</i> associated with current child hair mercury levels (Davidson et al 1998). In the Faroe Islands birth cohort study, language scores (Boston Naming Test) were not associated with current child hair or blood mercury levels (Grandjean et al 1997, 1998, 1999b, 2001b). A cross-sectional study in the former East Germany found no association between WISC vocabulary subtest scores and current urinary mercury levels (Walkowiak et al 1998).

Memory	<p>Low-level prenatal methylmercury exposure Limited</p> <p>Low-level postnatal methylmercury exposure (Inadequate)</p>	<p>Verbal, visual-spatial and visual-motor memory scores at age 7 years in the Faroe Islands birth cohort study were inversely associated with cord blood and marginally with prenatal maternal hair mercury levels (Weihe et al 1996, Grandjean et al 1997, 1999b, 2001b). The association between memory scores and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). When limited to Faroese children for whom mercury levels in two prenatal maternal hair segments were available and consistent, long-term verbal memory scores at age 7 years were still inversely associated with cord blood mercury levels (Grandjean et al 2003). Data from the Faroe Islands birth cohort study on verbal memory scores at age 7 years yielded a BMDL of 4.8 µg/g for prenatal maternal hair mercury (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). The Seychelles Islands cohort study found an inverse association between verbal memory subtest scores and prenatal maternal hair mercury levels; Boston Naming test scores were <i>positively</i> associated with prenatal maternal hair mercury in boys but not girls (Davidson et al 2000). Verbal memory test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). A literature review by the United Nations Environment Programme (2002) concluded that there is some evidence that low-level prenatal methylmercury exposure can cause verbal memory deficits. A literature review concluded that prenatally exposed experimental animals had visual recognition memory deficits and abnormal auditory startle habituation (Watanabe and Satoh 1996).</p> <p>Long-term verbal memory scores at age 7 years in the Faroe Islands study were not associated with current child hair or blood mercury levels (Grandjean et al 1999b). In the Seychelles Islands birth cohort study, there was a <i>positive</i> association between nonverbal memory performance and current child hair mercury levels (Palumbo et al 2000). A small cross-sectional study of children age 6-7 years in Madeira found no association between memory test scores and maternal or child hair mercury levels (Murata et al 1999b). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found an inverse association between nonverbal memory scores and child hair mercury levels (Grandjean et al 1999a). A cross-sectional study of Amerindian children age 0-6 years in French Guiana found no association between scores on the Stanford-Binet memory test and maternal hair mercury levels (Cordier et al 2002).</p>
Attention	<p>Low-level prenatal methylmercury exposure Limited</p>	<p>In the Faroe Islands birth cohort study, sustained attention scores (Continuous Performance Test reaction times, WISC digit spans scores) at age 7 years were unfavourably associated with prenatal maternal hair and/or cord blood mercury levels (Dahl et al 1996, Grandjean et al 1997, 1999b, 2001b). The association between CPT reaction time and cord blood mercury persisted after adjustment for umbilical cord tissue PCB levels (the latter were available for about half of the cohort) (Grandjean et al 1997). The associations between attention scores and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye</p>

		<p>glasses and with adjustment for visual contrast sensitivity, also found unfavourable associations between CPT reaction times and WISC digit span scores at age 7 years and cord blood mercury levels (Grandjean et al 2001a). Data from the Faroe Islands birth cohort study on sustained attention scores at age 7 years yielded a BMDL of 2.2 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found a persistent association between CPT reaction times and cord blood mercury levels (Grandjean et al 2003).</p> <p>The Seychelles Islands birth cohort study found no association between attention scores at ages 7 or 9 years and prenatal maternal hair mercury levels (Myers et al 2000b, 2003). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found a statistically non-significant association between CPT reaction times and cord blood mercury levels (Weihe et al 2002). An expert panel review noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with attention deficits in two of three large epidemiologic studies (National Academy of Sciences 2000). A literature review by the United Nations Environment Programme (2002) concluded that there is some evidence that low-level prenatal methylmercury exposure can cause attention deficits.</p>
Attention	Low-level postnatal methylmercury exposure	<p>CPT reaction times and WISC digit span scores at age 7 years were not associated with current child hair or blood mercury levels (Grandjean et al 1999b). A small cross-sectional study of children age 6-7 years in Madeira found no association between attention scores and maternal or child hair mercury levels (Murata et al 1999b). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found an inverse association between WISC digit span attention scores and current child hair mercury levels (Grandjean et al 1999a). The Seychelles Islands birth cohort study found no association between inattention and current child hair mercury levels (Myers et al 2000b).</p>
Motor function	Low-level prenatal methylmercury exposure Limited	<p>The Faroe Islands birth cohort study found that fine motor function scores (finger tapping speed and hand-eye coordination errors) at age 7 years were unfavourably associated with prenatal maternal hair and/or cord blood mercury levels (Dahl et al 1996, Grandjean et al 1997, 1999b, 2001b). The association between finger tapping scores and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, found inverse associations between finger tapping speed but not hand-eye coordination errors at age 7 years and cord blood mercury levels (Grandjean et al 2001a). Data from the Faroe Islands birth cohort study on finger tapping speeds at age 7 years yielded a BMDL of 4.3 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands</p>

		<p>birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found persistent unfavourable associations between finger tapping speed and hand-eye coordination errors and cord blood mercury levels (Grandjean et al 2003).</p> <p>In a cohort study based on follow-up of children enrolled in the Seychelles Islands cross-sectional pilot study, motor function (grooved pegboard) scores at age 9 years were <i>positively</i> associated with prenatal maternal hair mercury levels (Davidson et al 2000). Motor efficiency and finger tapping speed test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). A small cross-sectional study of children age 6-7 years in Madeira found a borderline association between failed reciprocal motor coordination and prenatal maternal hair mercury; finger tapping speed not associated with maternal or child hair mercury (Murata et al 1999b). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found inverse associations between finger tapping speed and motor coordination and dexterity scores and current child hair mercury levels (Grandjean et al 1999a). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found an association between hand-eye coordination test errors and prenatal maternal hair mercury levels (Weihe et al 2002). An expert panel review noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with fine-motor function deficits in two of three large epidemiologic studies; the panel noted evidence from experimental animal studies for motor deficits from low-dose prenatal methylmercury exposure (National Academy of Sciences 2000).</p>
Motor function	Low-level postnatal methylmercury exposure (Inadequate)	After adjustment for cord blood mercury, finger tapping scores at age 7 years in the Faroe Islands birth cohort study were not associated with postnatal mercury exposure as indicated by hair mercury levels at age 12 months or 7 years (Grandjean et al 1997, 1999b). A cross-sectional study of Amerindian children age 0-6 years in French Guiana found no association between finger tapping speed or leg coordination scores and maternal hair mercury levels (Cordier et al 2002).
Visual-motor integration	Low-level prenatal methylmercury exposure Limited	In the Seychelles Islands birth cohort study, visual-motor integration scores among children followed to ages 5 and 9 years were <i>positively</i> (i.e., favourably) associated with prenatal maternal hair mercury levels (Davidson et al 1998, 2000). Using continuous values of visual-motor function scores at age 5 years in the Seychelles Islands birth cohort study, the estimated benchmark dose lower limit (BMDL) for prenatal maternal hair was 27 µg/g (Crump et al 2000). Visual-motor integration test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). In the Faroe Islands birth cohort study, visuospatial function scores at age 7 years were not associated with prenatal maternal hair or cord blood mercury levels (Grandjean et al 1999b, 2001b). Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, also found no association between Bender Gestalt copying errors at age 7 years and cord blood mercury levels (Grandjean et al 2001a). Data from the Faroe

	Low-level postnatal methylmercury exposure (Inadequate)	<p>Islands birth cohort study on Bender Gestalt visuospatial scores at age 7 years yielded a BMDL of 6.8 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found an association between Bender Gestalt copying errors at age 7 years and cord blood mercury levels (Grandjean et al 2003). A literature review concluded that prenatal or postnatal methylmercury exposure affects high-order visual (contrast sensitivity, pattern recognition) systems at the cortical level (Newland 2002). An expert panel review noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with visual-spatial deficits in two of three large epidemiologic studies (National Academy of Sciences 2000).</p> <p>In the Faroe Islands birth cohort study, visuospatial function scores at age 7 years were not associated with current child hair or blood mercury levels (Grandjean et al 1999b, 2001b). A cross-sectional study of children age 7-12 years in the Amazon Basin found an inverse association between visuospatial function scores and child hair mercury levels (Grandjean et al 1999a). A cross-sectional study of Amerindian children age 0-6 years in French Guiana found no association between scores on the Stanford-Binet copying test of visuospatial organization and maternal hair mercury levels (Cordier et al 2002). A literature review concluded that prenatal or postnatal methylmercury exposure affects high-order visual (contrast sensitivity, pattern recognition) functions at the cortical level with effects being strongly age-dependent (Newland 2002).</p>
Visual-evoked potential latencies	<p>Low-level prenatal methylmercury exposure (Inadequate)</p> <p>Low-level prenatal methylmercury exposure (Inadequate)</p>	<p>A small retrospective cohort study of Inuit children age 7-12 years in Greenland found no association between brainstem visual-evoked potential latencies and prenatal maternal hair mercury levels (Weihe et al 2002). There was no association between visual-evoked potential latencies at age 7 years and cord blood mercury in the Faroe Islands birth cohort study (Grandjean et al 1997).</p> <p>A cross-sectional study in Germany found that no association between visual-evoked brainstem potential latencies at age 7 years and current urinary mercury levels (Altmann et al 1998). In a cross-sectional study of children age 6-7 years in Madeira, 1 of 4 measured pattern-reversal visual evoked potential latencies was associated with current maternal but not child hair mercury levels (Murata et al 1999b).</p>
Other visual function tests	(Inadequate)	A cross-sectional study in Germany found that contrast sensitivity (an indicator of visual cortical function) at age 5-7 years was inversely associated with current urinary mercury levels (Altmann et al 1998).
Auditor-evoked potential latencies and interpeak	Low-level prenatal methylmercury	Brain stem auditory-evoked potential latencies and interpeak intervals among children at ages 7 and 14 years were associated with prenatal maternal hair and cord blood mercury levels in the Faroe Islands

intervals	<p>exposure (Limited)</p> <p>Low-level postnatal methylmercury exposure (Inadequate)</p>	<p>birth cohort study (Grandjean et al 1997, Murata et al 1999b, 2004). Analysis of combined from children in the Faroe Islands and Madeira studies yielded a benchmark dose for prenatal maternal hair mercury of 9.5 µg/g for a doubling of a 5% prevalence of abnormal auditory-evoked potential latencies at 40 Hz, with similar results at 20 Hz (Murata et al 2002). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found associations between brainstem auditory-evoked potential latencies and prenatal maternal hair mercury levels (Weihe et al 2002).</p> <p>Brain stem auditory-evoked potential latencies and interpeak intervals among children at ages 7 and 14 years were not associated with current child hair mercury levels in the Faroe Islands birth cohort study (Grandjean et al 1997, Murata et al 1999b, 2004). Brain stem auditory-evoked potential latencies were associated with current maternal but not current child hair mercury levels in a cross-sectional study of children age 6-7 years in Madeira (Murata et al 1999a). Reports from a small cross-sectional study of Ecuadoran children age 3-15 years indicated associations between certain brainstem auditory-evoked potential latencies and intervals and current blood mercury levels (Counter et al 1998, 2003).</p>
Other auditory function indices	Low-level methylmercury exposure (Inadequate)	In the Seychelles Islands pilot study, reevaluation of a subgroup of children at age 5 years showed that the auditory comprehension scores were inversely associated with prenatal maternal hair mercury levels (Myers et al 1995a). A small cross-sectional study of Ecuadoran children age 3-15 years found an inverse (i.e., favourable) association between hearing threshold at 3 kHz in the right ear, but not in left ear, and current blood mercury levels (Counter et al 1998). A literature review concluded that prenatal or postnatal methylmercury exposure affects auditory systems at the cortical level (Newland 2002).
Academic performance	<p>Low-level prenatal methylmercury exposure (Inadequate)</p> <p>Low-level postnatal methylmercury exposure (Inadequate)</p>	<p>A reanalysis of a New Zealand birth cohort study found that reading concept, grammar completion and understanding scores at ages 6-7 years were inversely associated with prenatal maternal hair mercury levels (Crump et al 1998). In the Seychelles Islands birth cohort study, there were no associations between applied problem test scores at age 9 years and prenatal maternal child hair mercury levels (Myers et al 2000b, 2003).</p> <p>A birth cohort study in Michigan found an association between poor spelling scores at age 11 years and current hair mercury levels (Jacobson and Jacobson 1996). In the Seychelles Islands birth cohort study, applied problem scores at ages 5 years were <i>positively</i> associated with current hair mercury levels (Davidson et al 1998).</p>
Problem behaviours	Low-level prenatal methylmercury exposure (Inadequate)	The Seychelles Islands birth cohort study found no associations between aggressive and other problem behaviours and prenatal maternal hair mercury levels (Myers et al 2000b). Hyperactivity among Seychellois children age 9 years was inversely, i.e., favourably, associated with prenatal maternal hair mercury levels (Myers et al 2003).

	Low-level prenatal methylmercury exposure (Inadequate)	The Seychelles Islands birth cohort study found no associations between aggressive and other problem behaviours and current child hair mercury levels (Myers et al 2000b).
General: adverse health effects of methylmercury		An EPA report to Congress concluded that neurotoxicity is the most sensitive indicator of toxicity from elemental and organic mercury, the main effects in humans and multiple animal species being motor and sensory, especially sensorimotor integration (U.S. Environmental Protection Agency 1997). The latter report also concluded that the reference dose (RfD) for methylmercury, based on Iraqi data for developmental milestone delay in prenatally exposed children, was 0.1 µg/kg/day. After adjustment for cord blood mercury levels in the Faroe Islands birth cohort study, none of the neuropsychologic test scores at age 7 years was associated with current child hair mercury levels, i.e., the associations were with prenatal but not postnatal methylmercury exposure (Grandjean et al 1997). A literature review concluded that high-level prenatal methylmercury exposure disrupts neuronal proliferation and migration, causing widespread damage in the developing brain and the clinical appearance of cerebral palsy; only the most severely poisoned cases having peripheral nerve damage (Clarkson 1997). Another review stated that prenatal maternal consumption of marine fish from non-industrially polluted regions does not cause adverse neurodevelopmental outcomes (Myers and Davidson 1998). A summary of the 1997 EPA report to Congress noted that there is a steep dose-response relationship between methylmercury and neurotoxicity in experimental animals; subclinical toxicity occurs at 1.1 µg/g in diet, ataxia at 1.8 µg/g and death at 4.8 µg/g (Mahaffey 1999). An expert panel concluded that animal studies show cognitive, motor and sensory deficits from low-dose prenatal methylmercury exposure (National Academy of Sciences 2000).
General: adverse health effects of elemental mercury		A literature review concluded that the main sources of childhood exposure to elemental mercury have been accidental spills indoors and dental amalgam (a mixture of elemental mercury and other elements) and that there are no proven health effects of dental amalgam (Clarkson 1997).
Acrodynia	High-dose exposure to inorganic or elemental mercury Sufficient	This pediatric condition is characterized by pink hands and feet, desquamation, scarlet cheeks and other signs/symptoms; sporadic cases have been caused by exposure to mercurous chloride (calomel), teething powders or worm pills containing mercurous chloride, ammoniated mercury ointment and mercury bichloride used to rinse diapers (see Warkany and Hubbard 1951 below). A case of acrodynia in a boy age 5 years was linked to substantially elevated indoor air elemental mercury levels (210 µg/m ³) in a house painted with latex paint containing phenyl mercuric propionate; the child's urinary mercury level was 90 µg/L (Younglai et al 1998). A literature review concluded that inorganic mercury can cause acrodynia in children (Clarkson 1997).

Male fertility	(Inadequate)	A small cohort study found no association between a crude index of male fertility (number of children) and occupational exposure to airborne elemental mercury (Lauwerys et al 1985). A retrospective cohort study in Italy found an inverse association between likelihood of conception and preconceptional paternal occupational mercury exposure (Spinelli et al 1997).
Female fertility	(Inadequate)	A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced female fertility and occupation in dental offices (likely exposures to elemental mercury and nitrous oxide) (Paul 1997).
Semen quality	(Inadequate)	A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced semen quality and occupational exposure to inorganic mercury (Paul 1997).
Kidney function abnormalities	Low-level mercury exposure (Limited)	A small cross-sectional study of youth age 17-22 years found no association between urinary protein levels and number of amalgam tooth surfaces or urinary mercury levels (Herrstrom et al 1995). A larger cross-sectional study of children age 8-12 years in France found no association between urinary proteins and urinary mercury levels (Barbure et al 2003).
	High-level mercury exposure Sufficient	A cross-sectional study of infants exposed to diapers treated with a phenyl mercuric fungicide in Argentina found an association between urinary γ -glutamyl transpeptidase and urinary mercury excretion rates with an apparent threshold of about 6 $\mu\text{g}/\text{kg}$ body wt/day (Gotelli et al 1985). A literature review noted that childhood inorganic mercury exposure caused renal toxicity (Clarkson 1997).
Immune function	(Inadequate)	In two small Swedish cross-sectional studies of youth, plasma IgA and IgG ₂ levels were associated with plasma mercury levels (Herrstrom et al 1994, 1997). A history of allergic disease was not associated with plasma mercury (Herrstrom et al 1994). A birth cohort study in the Netherlands found no associations between immune function indices and current urinary mercury levels (Ten Tusscher et al 2003). A review of toxicologic literature concluded that inorganic mercury induces antibodies against renal glomerular basement membrane and renal deposition of immune-complexes (Powell et al 1999).
Cardiovascular abnormalities: blood pressure	(Inadequate)	The Faroe Islands birth cohort study found that diastolic and systolic blood pressure among children age 6-7 years were associated with cord blood mercury levels (Sorensen et al 1999). The EPA report to Congress and two other expert panel reviews found limited epidemiologic evidence that childhood blood pressure was associated with low-level prenatal methylmercury exposure (U.S. Environmental Protection Agency 1997, National Academy of Sciences 2000, United Nations Environment Programme 2002). Follow-up of Faroese children to age 14 years showed no associations between diastolic or systolic blood

		pressure and cord blood or childhood hair mercury levels (Grandjean et al 2004).
Cardiovascular abnormalities: heart rate variability	Limited	The Faroe Islands birth cohort study found that heart rate variability in boys was inversely associated with cord blood mercury (Sorensen et al 1999). The EPA report to Congress and two other expert panel reviews found limited epidemiologic evidence that childhood heart rate variability was associated with low-level prenatal methylmercury exposure (U.S. Environmental Protection Agency 1997, National Academy of Sciences 2000, United Nations Environment Programme 2002). Follow-up of Faroese children to age 14 years showed that heart rate variability was inversely associated with cord blood but not childhood hair mercury levels (Grandjean et al 2004).
Thyroid function	(Inadequate)	A cross-sectional study of children age 7-10 years in Germany found no association between thyroid hormone levels (TSH, T3, T4) and urine mercury levels (Osius et al 1999).
Genotoxicity: mutagenicity	Limited	A birth cohort study in Sweden found an increased risk of chromosomal abnormalities among infants of women who lived near a smelter that emitted mercury and other toxicants (Wulff et al 1996). The EPA report to Congress on mercury concluded that inorganic mercury is a possible germ cell mutagen a probable human germ cell mutagen (U.S. Environmental Protection Agency 1997).
Cancer	(Inadequate)	The EPA report to Congress on mercury concluded that inorganic and organic mercury are possible human carcinogens (U.S. Environmental Protection Agency 1997). Other expert panels concluded that there is inadequate evidence for carcinogenicity of methylmercury (National Academy of Sciences 2000, United Nations Environment Programme 2002). No epidemiologic studies have assessed the potential role of prenatal or childhood mercury exposure in childhood or adult cancers.
Atopic eczema	(Inadequate)	A cross-sectional study of children age 5-14 years found no associations between atopic eczema and urinary or blood mercury levels (Schafer et al 1999).
Elemental mercury poisoning	Indoor elemental mercury Sufficient	The health effects of mercury vapor have been known since ancient times with high exposure causing three major signs, i.e., skin rash, tremor and gingivitis (Clarkson 1997). There continue to be sporadic reports of clinically apparent childhood mercury poisoning caused by indoor exposure to elemental mercury vapour (Centers for Disease Control and Prevention 1995). In the USA during 2002, there were 9723 reports of children age 0-19 years who were exposed to elemental mercury from various sources including thermometers; among all elemental mercury exposure reports (persons of all ages), about 2% had moderate or severe health outcomes (Watson et al 2003). The latter data came from the Toxic Exposure Surveillance System (TESS) based on data from 64 participating US poison centers.
Autism	(Inadequate)	A small hospital-based case-control study in North America and the UK found an <i>inverse</i> association

		between autism among children age 2-15 years and current hair mercury levels (Holmes et al 2003). Another case-control study found no association between autism and current blood or hair mercury levels (Ip et al 2004).
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^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, found 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 found little or no evidence of exposure-risk relationships. Levels in parentheses are the author's interpretation of available evidence; other levels are based on expert group reviews.

2. Adverse pregnancy outcomes

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Elwood and Coldman 1981), Canada	Case-control study, 468 stillbirths caused by anencephaly, 4129 live birth controls, mothers resident in 142 communities population 10,000 or greater	Measured drinking water calcium, magnesium, copper, zinc, nickel, lead, selenium, mercury, chromium, silver, cobalt, cadmium and molybdenum levels for each community	Anencephaly <i>inversely</i> associated with drinking water mercury level in bivariate analysis; mean levels, cases vs controls	7.1 vs 8.0 µg/L, p<0.05		
			Anencephaly not associated with drinking water mercury level in multivariate analysis (result stated without supporting data)			Discriminant score based on linear discriminant function of 9 covariates: plurality of birth, legitimacy, season and year of birth, maternal age, birthplace, previous numbers of live births and stillbirths and child deaths; longitude of maternal residence
(Zierler et al. 1988), Massachusetts	Case-control study, 270 cases cardiac birth defects, 665 live birth controls	Assessed maternal exposure to mercury and 10 other chemicals in drinking water in communities where the mothers resided during pregnancy; median mercury level was 0.1 µg/L, 90 th percentile was 0.5 µg/L, highest level was 100 µg/L	Borderline weak association between any cardiac birth defect and drinking water mercury level (odds ratio, detectable vs no detectable mercury)	1.2 (0.9-1.6)		Other chemicals in drinking water, drinking water source, maternal SES
			Borderline association between patent ductus arteriosus and drinking water mercury level (odds ratio, detectable vs no detectable mercury)	1.6 (1.0-2.6)		

(Aschengrau et al. 1989), Massachusetts	Case-control study, 286 cases of early fetal deaths (spontaneous abortion), 1391 live birth controls	Measured trace element levels in drinking water supplies for communities where women lived while pregnant; mercury levels were all quite low (< 1.1 µg/L)	Borderline association between early fetal death and drinking water mercury levels (odds ratio, ≥ 0.2 µg/L vs undetectable)	1.5 (1.0-2.3)	Water source, maternal age, maternal education, previous spontaneous abortion
(Grandjean and Weihe 1993), Faroe Islands	Birth cohort study, 997 infants; assessed risk factors for low birth weight including maternal diet, alcohol, tobacco	Median cord blood mercury 24 µg/L, 75 th percentile 40 µg/L	Borderline <i>positive</i> association between birth weight and cord blood mercury among non-smoking women; birth weight increment for infants with cord blood >40 vs ≤ 40 µg/L	113g, p=0.07	Maternal prenatal fish consumption
(Aschengrau et al. 1993), Massachusetts	Hospital-based case control study, 1,039 birth defects, 77 late fetal deaths (stillbirths), 1,177 controls; drinking water quality data for water supply used at maternal residence during 1 st trimester	Water quality data included source, disinfection method, and chemical analyses including mercury; median level 0.2 µg/L, 90 th percentile 0.3 µg/L, highest level 1.1 µg/L	No association between late fetal deaths and drinking water mercury level (odds ratio, detectable vs non-detectable mercury)	0.7, p > 0.05	
			No association between total birth defects and drinking water mercury level (odds ratio, detectable vs non-detectable mercury)	1.1, p>0.05	
			Birth defects of skin not associated with drinking water mercury level (odds ratio, detectable vs non-detectable mercury)	1.2	Maternal race, age, insurance, previous infant with birth defect, prenatal alcohol, water source

(Marsh et al. 1995), Peru	Birth cohort study, 131 infants; assessed birth weight, height and head circumference, neurologic status, and ages at sitting, standing, walking and talking	Prenatal maternal hair GM mercury 7.1 (range 0.9-29 µg/g)	Birth weight, height and head circumference not associated with prenatal maternal hair mercury (pos = positive correlation, neg = negative correlation)	birth weight neg, p=0.27 height neg, p=0.11 head circumference neg, p=0.33		
(Bjerregaard and Hansen 1996), Greenland	Retrospective cohort study; 1,106 singleton live births; assessed risk factors for low birth weight	Maternal and cord blood mercury; average maternal and cord blood mercury levels, respectively, were 14.9 and 26.4 µg/L	Borderline inverse association between birth weight and maternal blood mercury; change in birth weight per maternal blood mercury increment of 10 µg/L	-18g, p=0.09		Maternal smoking, geographic region, ethnicity (Inuit vs. Dane)
(Wulff et al. 1996), Ronnskar Sweden	Birth cohort study; 120 birth defects among 2,724 births in population living near copper smelter and 582 birth defects among 15,191 births in comparison region	High environmental levels of lead, arsenic, cadmium, mercury; exposure index was residential proximity to copper smelter	No increased risks of birth defects observed in smelter region (relative risk, smelter vs comparison region)	1.2 (1.0-1.4)		
(Seidler et al. 1999), Germany	Birth cohort study, 3216 pregnant women, enrolled during gestation wk 15-28, 1987-1988; physician-reported pregnancy outcome history, 194 SGA infants	Self-reported maternal occupational history; job-exposure matrix to assess exposure to organic solvents, carbon tetrachloride, herbicides, chlorophenols, polychlorinated biphenyls,	SGA infants associated with maternal occupational mercury exposure (odds ratio, low exposure vs unexposed)	1.8 (1.1-2.6)		Maternal age, smoking, alcohol, BMI, parity

		aromatic amines, lead and lead compounds, mercury and mercury115 compounds				
(Grandjean et al. 2001c), Faroe Islands	Birth cohort, 182 pregnant women with spontaneous singleton births; assessed gestation length and birth weight	Measured cord blood fatty acids, PCBs and mercury	Birth weight not associated with cord blood mercury levels (mean birth weight by increasing cord blood mercury tertile; p-value from regression analysis with birth weight as continuous variable)	3643, 3662, 3661 g, p=0.63		Infant sex, parity, gestation length, maternal smoking, height, cord serum eicosapentanoic acid
			Gestation length not associated with cord blood mercury levels (mean gestation length by increasing cord blood mercury tertile; p-value from regression analysis with gestation length as continuous variable)	281.2, 280.1, 280.8 days, p=0.81		
(Grandjean et al. 2003b), Faroe Islands	Birth cohort study, 182 singleton term infants; measure height and weight at ages 18 and 42 mos	Breast milk PCB levels (non-coplanar congeners 138, 153, 180), cord blood mercury levels	Body weight at age 18 mos inversely associated with cord blood mercury (weight difference for a doubling of cord blood mercury)	-0.19 kg (-0.35, -0.03)	+	Birth weight, gestational age, sex, parity, maternal weight and height, diabetes, smoking, alcohol, child's age
		Multiple regression results suggest that PCBs and mercury may act independently	Height at age 18 mos inversely associated with cord blood mercury (height difference for a doubling of cord blood mercury)	-0.26 cm (-0.55, 0.02)	(+)	As above

^a Odds ratio or relative risk; + means that a statistically significant association or dose-response relationship was demonstrated

Adverse pregnancy outcomes: summary*Fetal death*

Case-control studies in Massachusetts found a borderline association between early fetal deaths (spontaneous abortions) (Aschengrau et al 1989) but not late fetal deaths (stillbirths) (Aschengrau et al 1993) and detectable mercury levels in drinking water in the community of maternal residence. A small birth cohort study in North Carolina found no excess fetal deaths (Elghany et al 1997). An expert panel concluded that prenatal methylmercury exposure causes fetotoxicity in mice (World Health Organization 1990).

Birth weight (unadjusted for gestation length)

A birth cohort study in the Faroe Islands found a borderline *positive* association between birth weight and cord blood mercury levels among non-smoking women (Grandjean and Weihe 1993). A small birth cohort study in Peru found no association between birth weight and prenatal maternal hair mercury levels (Marsh et al 1995). A retrospective cohort study in Greenland found a borderline inverse association between birth weight and prenatal maternal blood mercury levels (Bjerregaard and Hansen 1996).

Birth weight adjusted for gestation length

A German birth cohort study found an association between small for gestational age infants and maternal prenatal occupation exposure to mercury or mercury compounds (Seidler et al 1999). A small birth cohort study in the Faroe Islands found no association between birth weight adjusted for gestation length and cord blood mercury levels among singleton spontaneous live births (Grandjean et al 2001c).

Gestation length

A small birth cohort study in the Faroe Islands found no association between gestation length and cord blood mercury levels among singleton spontaneous live births (Grandjean et al 2001c).

Total birth defects

A large case-control study in Massachusetts found no association between total birth defects and drinking water mercury levels in the community of maternal residence (Aschengrau et al 1993). A retrospective birth cohort study found no increased risk of birth defects among infants of women living near a copper smelter in Sweden that emitted mercury and other toxicants (Wulff et al 1996). A small birth cohort study in North Carolina found a statistically non-significant excess of birth defects among women occupationally exposed to airborne elemental mercury (Elghany et al 1997). An expert panel concluded that prenatal methylmercury exposure causes birth defects in rats (World Health Organization 1990).

Specific birth defects

A large case-control study of anencephaly (a neural tube birth defect) in Canada found no association with drinking water mercury levels in the community of maternal residence (Elwood and Coldman 1981). A case-control study of cardiac birth defects in Massachusetts found a borderline association between patent ductus arteriosus and drinking water mercury levels in the community of maternal residence (Zierler et al 1988).

Postnatal growth

A small birth cohort study in the Faroe Islands found inverse associations between height and weight at ages 18 and 42 months and cord blood mercury levels, independent of duration of breastfeeding (Grandjean et al 2003b).

3. Delayed milestones

Reference, location	Design	Exposure	Results	Association	DR	Covariates
(Harada 1977), Japan	Review of 16 Minamata congenital methylmercury poisoning cases born during 1955-1959; follow-up to 1970	Mothers ingested methylmercury-contaminated seafood while pregnant; infant hair mercury level (1959-61) was 5.3-100 µg/g; prenatal maternal hair mercury (1959) was 1.8-191 µg/g	Age 1-2 yr: most infants had not achieved several developmental milestones (abilities to sit alone, walk alone, and speak), had abnormal reflexes, increased muscle tone and excessive salivation and displayed involuntary movements			
			Age 3 yr: none could understand maternal speech and most could not walk			
			Age 9-14 yr: only half could walk alone and all had speech impairment			
(Marsh et al. 1980), Iraq	Case series, 29 mother-infant pairs, infants exposed prenatally to methylmercury from maternal consumption of contaminated bread; infants followed to age 4-5 yr	Median peak prenatal maternal hair mercury was 25 µg/g (range 2-384)	Infants of mothers with the highest prenatal hair mercury levels (99-384 µg/g) had delayed motor and speech development; odds ratios, peak prenatal maternal hair mercury ≥99 vs <99 µg/g (calculated from data in paper)	delayed motor 5.0 (1.1-24) delayed speech 48 (4.5-1113)		
(Amin-Zaki et al. 1981), Iraq	Case series, 5-year follow-up of 29 infants postnatally exposed to methylmercury through breastfeeding and/or diet;; neurologic, ophthalmologic and	Two-thirds of mothers had blood mercury levels of at least 1000 µg/L at the end of the exposure period of 1-3 mos; 40% of infants had blood mercury levels of at	Non-significant association between delayed motor development (based on ages at sitting, standing, walking) and methylmercury exposure before age 10 mos; odds	2.8 (0.3-79)		

	otolaryngologic examinations, Gesell's developmental milestone screening tests	least 400 $\mu\text{g/L}$ when first tested	ratio, <10 vs 10+ mos (calculated from Table 1 in paper)			
(World Health Organization, 1990)	WHO health criteria for mercury	Methylmercury causes neurotoxic effects in all animal species studied with the fetus being more sensitive than adults	Extrapolation of Iraqi data suggest increased risk of delayed developmental milestones at prenatal maternal hair mercury levels as low as 10-20 $\mu\text{g/g}$			
(Grandjean et al. 1995), Faroe Islands	Hospital-based birth cohort study, 583 infants; assessed developmental milestones (sitting, creeping, standing) up to age 12 mos	Total mercury in prenatal maternal hair at delivery GM 4.5 $\mu\text{g/g}$, 15% $\geq 10 \mu\text{g/g}$; cord blood mercury range up to 174 $\mu\text{g/L}$; total mercury in infant hair at age 12 mos GM 0.7-1.9 $\mu\text{g/g}$, directly correlated with breast-feeding duration	Ages at sitting, creeping and standing <i>inversely</i> associated with hair mercury level at age 12 mos; Spearman correlation coefficients	sitting $r_s = -0.10$, $p = 0.01$ creeping $r_s = -0.13$, $p = 0.001$ standing $r_s = -0.10$, $p = 0.02$	+	
			Early milestone achievement associated with breastfeeding duration			Note: reduced breast-feeding duration associated with maternal smoking, single marital status, low birth weight, preterm birth and delivery complications
(Marsh et al. 1995), Peru	Birth cohort study, 131 infants; assessed birth weight, height and head circumference, neurologic	GM prenatal maternal hair mercury was 7.1 $\mu\text{g/g}$ (range 0.9-29)	Ages at sitting, standing, walking and talking not associated with peak prenatal maternal hair mercury levels	sitting pos, $p = 0.14$ standing		

	status, and ages at sitting, standing, walking and talking		(pos = positive correlation, neg = negative correlation)	pos, p=0.27 walking pos, p=0.33 talking pos, p=0.69		
(Myers et al. 1997), Seychelles Islands	Birth cohort study, 779 infants at age 6 mos and 738 at age 19 months; care-giver information on ages at walking and talking; analyzed full and partial multiple regression models	Median prenatal maternal hair mercury 5.9 (range 0.5-27 µg/g)	Partial model found a borderline association between age at walking and maternal prenatal hair mercury in boys but not girls; p-values for regression slope	boys p=0.04 girls p=0.94	+	Child sex, birth weight, medical history, maternal age, education, HOME score, language spoken at home
			Full model for age at talking was not significant	R ² =0.05, p=0.19		As above
(Clarkson 1997)	Literature review	Methylmercury – the main sources of exposure are marine fish and fish-eating mammals and freshwater fish	The Iraq data suggest that low-level prenatal methylmercury exposure may cause delayed developmental milestones at prenatal maternal hair mercury levels of 10-20 µg/g but there is considerable uncertainty about these levels			
(Axtell et al. 1998), Seychelles Islands	Birth cohort study, 738 infants age 19 mos; assessed age at walking and talking; analyzed relationships between age at walking and talking and prenatal maternal hair mercury using general additive models	Median prenatal maternal hair mercury 5.9 (range 0.5-27 µg/g)	Age at walking associated with prenatal maternal hair mercury levels in boys but not girls; p-values for mercury term	boys p=0.03 girls p=0.74	+	Child sex, birth weight, medical history, maternal age, education, HOME score, language spoken at home

			Smoothed mercury term associated with increase in log of age at walking as mercury increased from 0 to 7 µg/g and a slight decrease as mercury increased from 7 to 25 µg/g			
			No association between age at talking and prenatal maternal hair mercury levels			As above
(Newland 2002)	Literature review		Gestational or lactational exposure can cause delayed developmental milestones			

Delayed milestones (ages at first sitting, walking, talking): summary

High-level prenatal methylmercury exposure

A review of congenital methylmercury poisoning at Minamata noted that most infants age 1-2 years could not sit or walk alone or talk, had abnormal reflexes, increased muscle tone and excessive salivation and displayed involuntary movements (Harada 1977). This study also found that none of the exposed children could understand maternal speech and most could not walk at age 3 years; only half could walk alone at age 9-14 years and all had speech impairment. Among children prenatally exposed to high doses of methylmercury in Iraq, delayed developmental milestones were associated with prenatal maternal hair mercury levels (Marsh et al 1980, 1981, 1987). An expert group convened by the World Health Organization (1990) concluded that extrapolation of Iraqi data suggest increased risk of delayed developmental milestones at prenatal maternal hair mercury levels as low as 10-20 µg/g.

High-level postnatal methylmercury exposure

Among postnatally exposed Iraqi infants, there was a statistically non-significant association between delayed milestones (ages at sitting, standing, walking) and lactational and/or dietary methylmercury exposure before age 10 months, compared to those exposed at older ages (Amin-Zaki et al 1981).

Relatively low-level prenatal methylmercury exposure

A birth cohort study in the Faroe Islands found no associations between age at milestone development and prenatal maternal hair or cord blood mercury levels; moreover, *early* milestone development was associated with breastfeeding duration and infant hair mercury level at age 12 months (Grandjean et al 1995). A small birth cohort study in Peru found no associations between age at milestone development and prenatal maternal hair mercury levels (Marsh et al 1995). A birth cohort study in the Seychelles Islands found an association between age at walking and prenatal maternal hair mercury levels in boys but not girls; age at talking was not associated with prenatal maternal hair mercury (Myers et al 1997, Axtell et al 1998). Recent literature reviews concluded that delayed developmental milestones may occur at prenatal maternal hair mercury levels as low as 10-20 µg/g and noted the considerable uncertainty about this estimate (Clarkson 1997, 2002, Newland 2002).

4. Neurologic abnormalities

Reference, location	Design	Exposure	Results	Association	DR	Covariates
(Snyder 1971), USA	Case report, family of 10 exposed to methylmercury-contaminated meat; mother exposed during 2 nd trimester	Family consumed meat from pig fed methylmercury-treated seed grain	Prenatally exposed infant had gross tremors of extremities at birth, irritability and increased muscle tone at 6 wks, grossly abnormal EEG at 3 mos and generalized myoclonic jerks at 6 mos; mother had no symptoms			
			3 older siblings developed ataxia, agitation, visual impairment and impaired consciousness			
(Bakir et al. 1973), Iraq	Review of the 1972 Iraq methylmercury poisoning epidemic; included 20 mother-infant pairs with prenatal and/or lactational methylmercury exposure	Mean methylmercury level in wheat flour was 9.1 µg/g (range 4.8-15); 8 of 11 infants had blood mercury levels above 500 µg/L	Three prenatally exposed infants had the highest blood mercury levels and had signs of severe brain damage			
			Case fatality rate for hospitalized cases age 1-19 yr was 8%; 63% of all hospital deaths from methylmercury occurred among children and youth age <20 yr			
(Amin-Zaki et al. 1974), Iraq	Case series; 15 infants exposed prenatally and lactationally to methylmercury; interval since exposure was 1-11 mos	3 infants had blood mercury levels of at least 3,000 µg/L at end of exposure period	3 infants had microcephaly, 4 were completely blind and had severe hearing loss, 3 had spastic paralysis and 2 had flaccid paralysis			
			6 of the 15 mothers had one or more neurologic signs including headache, joint pain, paresthesias,			

			motor weakness, increased deep tendon reflexes, blurred vision, constricted visual fields, ataxia			
(Harada 1977), Japan	Review of 16 Minamata congenital methylmercury poisoning cases born during 1955-1959; follow-up to 1970	Mothers ingested methylmercury-contaminated seafood while pregnant; infant hair mercury level (1959-61) was 5.3-100 µg/g; prenatal maternal hair mercury (1959) was 1.8-191 µg/g	5/16 neonates found irritability, 1 had convulsions			
			At age 1-7 yr, all had impaired chewing/swallowing, speech, gait, coordination and mental development, inability to walk by oneself, increased muscle tone and incontinence			
			At age 9-14 yr, all were mentally retarded (IQ<75) and still had muscle spasticity, ataxia and athetoid movements			
(Harada 1978), Japan	Review of Minamata methylmercury poisoning episode, 13 severe cases among 220 infants born during 1955-1958, 40 cases in wider region by 1976	Methylmercury-contaminated seafood; prenatal maternal hair samples first collected 2-5 years after births had elevated mercury levels (values not given)	Infants normal at birth; neurologic abnormalities started to appear at age 6 mos and included primitive reflexes, ataxia, strabismus, dysarthria, hyperkinesia, hypersalivation, cerebral palsy			
			Mothers had no abnormal neurologic abnormalities during pregnancy or at birth; 28 mothers later developed one or more abnormalities including			

			paresthesias, mild incoordination, constriction of visual fields, dysarthria and tremor			
(Amin-Zaki et al. 1978), Iraq	Case series, 49 children age 2-16 yr, exposed postnatally to methylmercury-contaminated bread; 2-year follow-up	Blood mercury half life was 56 days (range 39-72); blood mercury levels at end of exposure period ranged from about 2 to 30 µg/L (estimated from Figure in paper)	Severity and persistence of ataxia, weakness and visual and sensory deficits associated with blood mercury concentration			
			Children with mild/moderate poisoning slowly improved but all had persistent hyperreflexia			
			Visual changes improved but less completely – among 17 blind children, only 5 recovered partial sight			
			7/18 children with severe poisoning had persistent physical and mental disability			
(Amin-Zaki et al. 1979), Iraq	Case series; 32 prenatally exposed mother-infant pairs; followed for 5 years	Peak maternal prenatal hair mercury levels ranged from 32 to 592 µg/g; infant blood mercury levels before age 2 mos were 42-4220 µg/L (at variable intervals since end of exposure)	Mothers of 8 of 9 cerebral palsy infants and 0 of 10 non-cerebral palsy infants had 3 rd trimester peak hair mercury levels; mean maximum 3 rd trimester prenatal maternal hair mercury concentration was 444 µg/g for cerebral palsy cases	Fisher's p=0.03		
			Cerebral palsy not observed among the 10 infants of mothers whose peak hair mercury occurred			

			in 1 st trimester			
			15 of 27 examined mothers had one or more manifestations of methylmercury poisoning; women with neurologic abnormalities had higher peak prenatal hair mercury levels (analysis of variance p-value)	p<0.01		
(Marsh et al. 1980), Iraq	Case series, 29 mother-infant pairs, infants exposed prenatally to methylmercury from maternal consumption of contaminated bread; infants followed to age 4-5 yr	Median peak prenatal maternal hair mercury was 25 µg/g (range 2-384)	Infants of mothers with the highest prenatal hair mercury levels (99-384 µg/g) had mental retardation and seizures during infancy; odds ratios, peak prenatal maternal hair mercury ≥99 vs <99 µg/g (calculated from data in paper)	mental retardation 6.8 (0.9-61) seizures 11 (1.4-93)		
			Neurologic abnormalities occurred in some children whose mothers were asymptomatic during pregnancy			
(Marsh et al. 1981), Iraq	Case series, 84 mother-infant pairs; infants examined by neurologists who assessed presence of neurologic signs and symptoms	Prenatal ingestion of methylmercury-contaminated bread; peak prenatal maternal hair mercury 0.4-640 µg/g	Moderate and severe neurologic signs associated with peak prenatal maternal hair mercury level; odds ratio, ≥18 vs <18 µg/g (calculated from data in Table 2 in paper)	18 (2.9-403)		
			Severe psychomotor retardation among 5 children with peak prenatal maternal hair mercury levels of 165-320 µg/g during 2 nd trimester			

(Amin-Zaki et al. 1981), Iraq	Case series, 5-year follow-up of 29 infants exposed at age 1-10 mos to methylmercury through breastfeeding; neurologic, ophthalmologic and otolaryngologic examinations, Gesell's developmental milestone screening tests	Two-thirds of mothers had blood mercury levels of at least 1000 µg/L at the end of the exposure period of 1-3 mos; 40% of infants had blood mercury levels of at least 400 µg/L when first tested	Prevalence of hyperreflexia increased from 8/22 infants at 1 st examination to 17/22 at 2 nd examination; non-significant association between hyperreflexia and exposure before age 10 mos; odds ratio, <10 vs 10+ mos (calculated from Table 1 in paper)	3.6 (0.4-36)		
(McKeown-Eyssen et al. 1983), northern Quebec	Cross-sectional study, 234 Cree Indian infants age 12-30 mos; conducted neurologic examination (coordination, cranial nerves, muscle tone, tendon reflexes) and Denver developmental scale (gross and fine motor, language and personal/social skill development)	Mean prenatal maternal hair mercury in segments corresponding to pregnancy was 6 µg/g (6% had levels ≥ 20 µg/g)	Abnormal muscle tone or reflexes associated with maximum prenatal maternal hair mercury in boys but not girls; odds ratio per prenatal maternal hair mercury increment of 10 µg/g	7.1 (1.0-51)		Age, breastfeeding duration, mother's age, maternal smoking, alcohol, caffeine consumption
(Marsh et al. 1987), Iraq	Case series, 81 mother-infant pairs; assessed neurologic status by clinical examination; assigned scores for abnormal signs – range of total scores from least to most severe was 0-11	Mothers prenatally exposed to methylmercury-contaminated bread; identified maximum prenatal maternal hair mercury levels	Adverse neurologic sign scores associated with peak prenatal maternal hair mercury levels; avg neurological scores for sons of mothers with peak prenatal hair mercury levels of <1, 1, 2-7, 8-19, 20-72, 73-196, 197-376, 377-674 µg/g; Pearson p-trend calculated from data in Table 2 in paper	males 0.43, 0.14, 0.00, 0.33, 1.14, 3.00, 2.80, 8.67 p-trend=0.02	+	
			Adverse neurologic sign scores associated with peak prenatal maternal hair mercury levels; avg neurological scores for daughters	females 0.50, 0.33, 0.00, 1.00, 0.33, 1.40,	+	

			of mothers with peak prenatal hair mercury levels of <1, 1, 2-7, 8-19, 20-72, 73-196, 197-376, 377-674 $\mu\text{g/g}$; Pearson p-trend calculated from data in Table 2 in paper	2.60, 5.25 p-trend=0.02		
(Harada 1995), Japan	Review of Minamata disaster; 17 severe cases of congenital Minamata disease/cerebral palsy in Minamata Bay fishing villages during 1955-1958; 47 milder cases not described	Mercury concentration in marine fish was 5.6-36 $\mu\text{g/g}$; prenatal maternal hair mercury levels ranged from 1.8 to 191 $\mu\text{g/g}$ when tested 5-8 yr after birth of affected infant	Neurologic abnormalities among most or all affected infants included mental retardation, primitive reflexes, cerebellar ataxia, dysarthria, hypersalivation, hyperkinesias, strabismus and spasticity			
(Myers et al. 1995b), Seychelles Islands	Birth cohort study, 779 infants age 6 mos; conducted neurologic assessment, Fagan test of visual recognition memory and Denver Developmental Screening Test-Revised (DDST-R); too few abnormal results on DDST-R for analysis	Median prenatal maternal hair mercury 5.9 $\mu\text{g/g}$ (range 0.5-27); only 5% of mothers used alcohol and only 2% smoked during pregnancy	Muscle tone and deep tendon reflexes at age 6 mos not associated with prenatal maternal hair mercury; β -coefficients	limb tone $\beta=-0.02\pm 0.12$ deep tendon reflexes $\beta=-0.15\pm 0.13$		Child sex, birth weight, birth order, gestational age, medical history, breastfeeding; maternal age, prenatal alcohol and tobacco use, medical history, maternal IQ, HOME score, family income, language spoken at home, parental education
(Marsh et al. 1995), Peru	Birth cohort study, 131 infants; assessed birth weight, height and head circumference, neurologic status, and ages at sitting, standing, walking and talking	Prenatal maternal hair GM mercury 7.1 $\mu\text{g/g}$ (range 0.9-29)	Increased reflexes (n=4) not associated with peak prenatal maternal hair mercury concentration; p-value from analysis of variance	p=0.18		
(Myers and	Literature review		High-level prenatal			

Davidson 1998)			methylmercury exposure causes mental retardation and cerebral palsy			
(Harada et al. 1999), Japan	Case series, 25 infants with congenital Minamata disease, 77 healthy infants from Minamata	Measured umbilical cord tissue mercury levels	Mean umbilical cord tissue mercury level, cases vs healthy infants	1.60±1.00 μg/g vs. 0.28±0.20 μg/g		
(Myers et al. 2000a; Myers and Davidson 2000)	Literature review		High-level prenatal methylmercury exposure can cause developmental disabilities (mental retardation, cerebral palsy, seizures)			
(Steuerwald et al. 2000), Faroe Islands	Birth cohort study, 182 births at one hospital during 1994-1995; measured a neurologic optimality score at age 2 wk by assessing functional abilities, muscle tone, reflexes, responses	Measured mercury in cord blood (GM 20 μg/L, range 12-40) and prenatal maternal hair (GM 4.1 μg/g, range 2.5-7.4)	Neurologic optimality score at age 2 yr inversely associated with cord blood mercury; regression coefficient	β=-2.0, p=0.03	+	
			Muscle tone subscore not associated with cord blood mercury (result stated without supporting data)			
(National Academy of Sciences 2000)	Literature review		High-dose prenatal methylmercury exposure causes mental retardation, cerebral palsy, deafness, blindness and dysarthria			
(Clarkson 2002)	Literature review		High-level prenatal maternal methylmercury ingestion can cause severe brain damage			

			Apparently normal Iraqi children exposed to methylmercury had delayed developmental milestones and neurologic abnormalities (hyperreflexia); there was an exposure-risk relationship between peak prenatal maternal hair mercury during gestation and risk of these effects			
(United Nations Environment Programme, 2002), Geneva	Literature review		Clear evidence for neurotoxicity of methylmercury at high exposure levels, especially for the developing brain			

Neurologic abnormalities summary

Mental retardation, cerebral palsy, seizures, deafness, blindness, dysarthria

High-level prenatal methylmercury exposure An infant prenatally exposed to methylmercury because the mother and family consumed meat from a pig fed methylmercury-treated seed grain had gross tremors of extremities at birth, irritability and increased muscle tone at postnatal week 6, grossly abnormal EEG at age 3 months and generalized myoclonic jerks at age 6 months; three older siblings developed ataxia, agitation, visual impairment and impaired consciousness but the mother had no symptoms (Snyder 1971). During the 1972 Iraq methylmercury poisoning episode, prenatally exposed infants had microcephaly and developed severe neurotoxicity including blindness, severely impaired hearing and generalized paralysis (Amin-Zaki et al 1974, 1979). Follow-up of prenatally exposed Iraqi infants found that cerebral palsy was associated with 3rd trimester exposure (Amin-Zaki 1979). Delayed motor and speech development and seizures during infancy were associated with high prenatal maternal hair and postnatal blood mercury levels (Amin-Zaki 1981, Marsh et al 1980, 1981). There were dose-response relationships between abnormal neurologic signs and peak prenatal maternal hair mercury levels with stronger associations among boys than girls (Marsh et al 1987). An expert panel concluded that prenatal methylmercury exposure causes severe neurotoxicity among infants of women with hair mercury levels above 400 µg/g (World Health Organization 1990). This panel also concluded that methylmercury causes neurotoxic effects in all animal species studied with the fetus being more sensitive than adults. Prenatally exposed infants at Minamata appeared normal at birth but neurologic abnormalities started to appear at age 6 months and included primitive reflexes, cerebellar ataxia, strabismus, dysarthria, hyperkinesia, hypersalivation, spasticity (i.e., cerebral palsy-like syndrome) and seizures (Harada 1977, 1978, 1995, Watanabe and Satoh 1996). At age 1-7 years, children with Minamata disease all had impaired chewing/swallowing, speech, gait, coordination and mental development, inability to walk alone, increased muscle tone and incontinence; at age 9-14 years, all were mentally retarded (IQ<75) and still had muscle spasticity, ataxia and athetoid movements (Harada 1977). Although maternal and cord blood or hair samples were not collected in Minamata, a retrospective study of infants with severe neurotoxicity revealed elevated umbilical cord tissue mercury levels (Harada et al 1999). In both Iraq and Minamata, mothers of infants with congenital methylmercury poisoning generally had mild or no symptoms during pregnancy but some later developed one or more abnormalities including paresthesias, mild incoordination, constriction of visual fields, dysarthria and tremor

(Harada 1978). Several literature reviews concluded that high-level prenatal methylmercury exposure causes severe neurotoxic effects in infants including mental retardation, cerebral palsy, seizures, deafness, blindness and dysarthria (Harada et al 1978, 1995, 1999, Myers and Davidson 1998, Myers et al 2000, Myers and Davidson 2000, National Academy of Sciences 2000, United Nations Environment Programme 2002, Clarkson 2002).

Ataxia, weakness and visual and sensory deficits

High-level postnatal methylmercury exposure Children postnatally exposed to methylmercury from a pig fed methylmercury-treated seed grain developed ataxia, agitation, visual impairment and impaired consciousness but the mother had no symptoms (Snyder 1971). Two-year follow-up of 49 children exposed at age 0-14 years during the Iraq methylmercury poisoning episodes, found that the severity and persistence of ataxia, weakness and visual and sensory deficits were associated with baseline blood mercury levels (Amin-Zaki et al 1978). Children with mild/moderate poisoning improved slowly but all had persistent hyperreflexia; 5 of 17 blind children recovered partial sight and 7 of 18 children with severe poisoning had persistent physical and mental disability.

Abnormal muscle tone, deep tendon reflexes

Low-level prenatal methylmercury exposure A cross-sectional study of Aboriginal infants age 12-30 months in northern Quebec found that abnormal tendon reflexes in boys but not girls were associated with maximum prenatal maternal hair mercury levels but there was no dose-response relationship (McKeown-Eyssen et al 1983). A birth cohort study of almost 800 infants in the Seychelles Islands found no association between muscle tone, deep tendon reflexes and overall neurologic status and prenatal maternal hair mercury levels (Myers et al 1995b). A small birth cohort study in Peru also found no associations between deep tendon reflexes and prenatal maternal hair mercury levels (Marsh et al 1995). A small birth cohort study in the Faroe Islands found that a neurologic optimality score, but not the muscle tone component of the score, was inversely associated with cord blood mercury levels (Steuerwald et al 2000).

5. Neuropsychologic deficits

Reference, location	Design	Exposure	Results	Association	DR	Covariates
(Myers et al. 1995a)	Cohort study, followed 217 children from cross-sectional pilot study to age 66 mos; conducted McCarthy Scales of Children's Abilities, Preschool Language Scale, and the Letter-Word Identification and Applied Problems subscales of the Woodcock-Johnson Tests of Achievement; multiple regression analysis	Median prenatal maternal hair mercury 7.1 $\mu\text{g/g}$ (range 1.0-36)	McCarthy general cognitive index inversely associated with prenatal maternal hair mercury; regression coefficient	$\beta=-0.55$, $p=0.02$	+	Child age, sex, birth weight, Apgar, medical history, maternal age, prenatal alcohol and tobacco use, medical history, SES
			Auditory comprehension inversely associated with prenatal maternal hair mercury; regression coefficient	$\beta=-0.23$, $p=0.002$	+	As above
(Myers et al. 1995b), Seychelles Islands	Birth cohort study, 779 infants age 6 mos; conducted neurologic assessment, Fagan test of visual recognition memory and Denver Developmental Screening Test-Revised (DDST-R); too few abnormal results on DDST-R for analysis	Median prenatal maternal hair mercury 5.9 $\mu\text{g/g}$ (range 0.5-27); only 5% of mothers used alcohol and only 2% smoked during pregnancy	Fagan visual recognition memory scores at age 6 mos not associated with prenatal maternal hair mercury levels (no measure of association given in paper)			Child sex, birth weight, birth order, gestational age, medical history, breastfeeding; maternal age, prenatal alcohol and tobacco use, medical history, maternal IQ, HOME score, family income, language spoken at home, parental education
			Fagan visual attention scores at age 6 mos not associated with			As above

			prenatal maternal hair mercury levels (no measure of association given in paper)			
(Davidson et al. 1995), Seychelles Islands	Birth cohort study, 738 infants at age 19 mos and 736 at age 29 mos; conducted BSID at both ages and Bayley Infant Behavior Record at 29 mos	Median prenatal maternal hair mercury 5.9 $\mu\text{g/g}$ (range 0.5-27)	Mental development index scores at ages 19 and 29 mos not associated with prenatal maternal hair mercury; partial R^2 values	age 19 mos $R^2=0.1$, $p>0.05$ age 29 mos $R^2=0.2$, $p>0.05$		Child sex, birth weight, medical history, maternal age, education, HOME score, language spoken at home
			Activity level at age 29 mos inversely associated with prenatal maternal hair mercury in boys but not girls; partial R^2 value	boys $R^2=1.3$, $p<0.01$ girls $R^2=0.005$, $p>0.05$	+	As above
(Dahl et al. 1996), Faroe Islands	Birth cohort study, 917 children age about 7 yr; conducted finger tapping, sustained attention (continuous performance), and hand-eye motor coordination tests	Median cord blood mercury was 24.2 $\mu\text{g/L}$; median prenatal maternal hair mercury was 4.5 $\mu\text{g/g}$	Finger tapping speed (preferred hand) inversely associated with prenatal maternal hair and cord blood mercury level; change in score per doubling of mercury concentration	prenatal maternal hair mercury -0.43, $p<0.05$ cord blood mercury -0.45, $p<0.05$	+	Age, sex, computer acquaintance, visual function
			Reduced performance on sustained attention test (longer CPT reaction times) associated with cord blood but not prenatal maternal hair mercury level; change in reaction time per doubling of mercury concentration	prenatal maternal hair mercury 4.0 msec, $p>0.05$ cord blood mercury 5.2 msec, $p<0.01$	+	As above

			Hand-eye coordination errors associated with prenatal maternal hair and cord blood mercury; increased errors per doubling of mercury concentration	<p>prenatal maternal hair mercury 0.02, $p < 0.05$</p> <p>cord blood mercury 0.015, $p < 0.05$</p>	+	As above
(Jacobson and Jacobson 1996), Michigan	Birth cohort study, 313 children at baseline (see Jacobson et al 1990 in PCB evidence table); conducted WISC-R and spelling, arithmetic and word/passag e comprehension tests on 212 children at age 11 yr	Serum samples at age 4 and 11 yr tested for PCBs, PBBs and 7 organochlorine pesticides (only DDT/DDE was detected); also measured blood lead at age 4 and 11 yr and hair mercury at age 11 yr	Poorer spelling scores at age 11 yr associated with current hair mercury level; p-value stated but no measure of association given in paper	$p = 0.006$	+	SES, maternal education and vocabulary, HOME score
(Grandjean et al. 1997), Faroe Islands	Birth cohort study, 917 children age 7 yr; tested visual acuity, conducted Child Behavior Checklist and tests of finger tapping, hand-eye coordination, tactual performance, Continuous Performance Test (CPT), WISC-R subtests, Bender Gestalt visual-motor, California verbal learning, Boston naming and mood tests	GM mercury in cord blood 23 $\mu\text{g/L}$ (range 13-41), prenatal maternal hair 4.3 $\mu\text{g/g}$ (range 2.6-7.7), child hair at 12 mos 1.1 $\mu\text{g/g}$ (range 0.7-1.9), child hair at age 7 yr 3.0 $\mu\text{g/g}$ (range 1.7-6.1)	Motor function: finger tapping speed (preferred hand) but not hand-eye coordination errors at age 7 yr inversely associated with cord blood mercury	<p>finger tapping speed $\beta = -1.10$, $p = 0.05$</p> <p>hand-eye coord errors $\beta = 0.03$, $p = 0.19$</p>	+	Age, sex, maternal IQ, obstetric and postnatal risk factors, daycare, parental education, paternal employment
			Attention: CPT reaction time (msec) and WISC digit spans score unfavourably associated with cord blood mercury; after	reaction time $\beta = 40.3$, $p = 0.001$	+	As above

			inclusion of cord tissue PCB levels, association between reaction time and cord blood mercury persisted ($\beta=-37.8$, $p=0.002$)	digit spans $\beta=-0.27$, $p=0.05$	+	
			Cognitive function: WISC similarity and block design scores not associated with cord blood mercury	similarity $\beta=-0.05$, $p=0.90$ block design $\beta=-0.17$, $p=0.11$		As above
			Language: Boston Naming test scores inversely associated with cord blood mercury (β -coefficient); after inclusion of cord tissue PCB levels, association with cord blood mercury was weaker ($\beta=-1.04$, $p=0.21$)	$\beta=-1.77$, $p=0.0003$	+	As above
			Memory: California verbal learning long-term memory score inversely associated with cord blood mercury; after inclusion of cord tissue PCB levels, association with cord blood mercury was weaker ($\beta=-1.78$, $p=0.11$)	$\beta=-0.55$, $p=0.05$	+	As above
			Important note: after excluding children for whom prenatal maternal hair mercury level exceeded 10 $\mu\text{g/g}$, the above associations persisted			

			After adjustment for cord blood mercury levels, no neuropsychologic score was associated with child hair mercury levels at ages 1 or 7 yr			
			Visual evoked potential latencies at age 7 yr not associated with cord blood mercury; β -coefficient, N75 latencies at 15'	$\beta=0.21$, $p=0.70$		Adjusted for age, sex; excluded children with strabismus or need for eye glasses
			Brain stem auditory evoked potential latencies associated with cord blood mercury; β -coefficient, peak III latency	$\beta=0.05$, $p=0.06$	(+)	As above
(U.S. Environmental Protection Agency 1997)	Literature review (report to Congress)		Neurotoxicity is the most sensitive indicator of toxicity from elemental and organic mercury – main deficits in humans and multiple species are motor and sensory, especially sensorimotor integration			
			RfD based on Iraqi data for late walking, late talking and neurologic scores was 0.1 $\mu\text{g}/\text{kg}/\text{day}$			
(Clarkson 1997)	Literature review	Methylmercury – the main sources of exposure are marine fish and fish-eating mammals and freshwater fish	Methylmercury selectively damages the developing and adult brain – only the most severely poisoned cases have peripheral nerve damage			

			By disrupting neuronal proliferation and migration, high-level prenatal methylmercury exposure causes widespread damage in the developing brain and the clinical appearance of cerebral palsy			
		Elemental mercury – the main sources of childhood exposure have been accidental spills indoors and dental amalgam	No proven health effects of dental amalgam			
			High-level prolonged exposure ($\geq 100 \mu\text{g}/\text{m}^3$) of adults causes nervous system damage			
(Grandjean et al. 1998), Faroe Islands	Birth cohort study, 112 matched pairs of children age 7 yr with contrasting prenatal maternal hair mercury levels; conducted fine motor (finger tapping, hand-eye coordination), attention (Continuous Performance Test (CPT), WISC-R Digit Spans subtest), executive function (WISC-R Similarities subtest), visuospatial function (WISC-R block designs, Bender Gestalt copy condition), language	For half of children, prenatal maternal hair mercury was 10-20 $\mu\text{g}/\text{g}$; for others, prenatal maternal hair mercury < 3 $\mu\text{g}/\text{g}$	Motor: finger tapping (preferred hand) speed and hand-eye coordination errors not associated with maternal prenatal hair mercury (median score, hair mercury 10-20 vs <3 $\mu\text{g}/\text{g}$)	finger tapping 42 vs 43, $p=0.14$ hand-eye errors 2.61 vs 2.60, $p=0.60$		Matched for age, sex, year of examination, maternal IQ

	(Boston naming), and short-term memory (California Verbal Learning, Bender Gestalt recall) tests					
			Attention: CPT reaction time and WISC digit spans not associated with maternal prenatal hair mercury (median score, hair mercury 10-20 vs <3 µg/g)	reaction time 750 vs 735, p=0.35 digit spans 4 vs 4, p=0.85		As above
			Cognitive function: WISC similarities and block design scores not associated with maternal prenatal hair mercury (median score, hair mercury 10-20 vs <3 µg/g)	similarities 7 vs 8, p=0.13 block design 13 vs 14, p=0.08	(+)	As above
			Language: borderline association between Boston naming test scores and maternal prenatal hair mercury (median score, hair mercury 10-20 vs <3 µg/g)	24 vs 25, p=0.06	(+)	As above
			Memory: California verbal learning long-term memory score not associated with maternal prenatal hair mercury (median score, hair mercury 10-20 vs <3 µg/g)	4 vs 5, p=0.07	(+)	As above
(Walkowiak et al. 1998), 3 cities in the former East Germany	Cross-sectional study, 384 children age 5-7 yr; conducted Functional Acuity Contrast Tests and 2 subtests of WISC (German	Geometric G GM urinary mercury 0.16 µg/day (range 0.02-2.83)	Cognitive function: WISC vocabulary and block design subtest scores not associated with urinary mercury; regression coefficients	vocabulary b=-0.22, p>0.05 block design		Various combinations of variables including age, birth weight, number of siblings,

	version), finger tapping, perceptual speed, reaction time, pattern memory and sustained attention tests			b=-0.09, p>0.05		height, nationality, education, sex, prenatal maternal smoking, duration of breastfeeding
			Motor function: finger tapping speed not associated with urinary mercury; regression coefficients	b=0.32, p>0.05		As above
			Attention: CPT reaction time not associated with urinary mercury; regression coefficients	b=4.3, p>0.05		As above
(Crump et al. 1998), New Zealand	New Zealand birth cohort study, 237 children age 6-7 years; estimated benchmark dose lower limits (BMDLs) by modeling associations between prenatal maternal hair mercury and continuous scores on 26 scholastic and psychologic tests	61 children of mothers with hair mercury ≥ 6 $\mu\text{g/g}$, 176 children of mothers with lower hair mercury levels matched for ethnicity, maternal smoking, urban/rural residence and duration of residence in New Zealand before child's birth	Estimated the 95% bench mark dose lower limits (BMDLs) of five neuropsychologic outcomes vs prenatal maternal hair mercury levels	<p>McCarthy perceptual scale 7.4 $\mu\text{g/g}$</p> <p>spoken language 9.5 $\mu\text{g/g}$</p> <p>McCarthy motor scale 9.8 $\mu\text{g/g}$</p> <p>WISC performance IQ 10 $\mu\text{g/g}$</p> <p>WISC full-scale IQ 10 $\mu\text{g/g}$</p>		

(Davidson et al. 1998), Seychelles Islands	Birth cohort study, 711 children age 66 mos; conducted general cognitive index subscale of the McCarthy Scales of Children's Abilities, the Preschool Language Scale, the Letter and Word Recognition test, the Applied Problems subtest of the Woodcock-Johnson Tests of Achievement, the Bender Gestalt test of visual-spatial ability, the Child Behavior Checklist	Mean prenatal maternal hair mercury 6.8 µg/g (range 0.5-27) and mean child current hair mercury 6.5 µg/g (range 0.9-26); measured serum PCBs for 49 children	Borderline inverse association between McCarthy general cognitive index at age 5 yr and current child but not prenatal maternal hair mercury; regression coefficients and std errors	child hair 0.26±0.14 maternal prenatal hair -0.06±0.10	(+)	Child sex, birth weight, birth order, gestational age, medical history, breastfeeding; maternal age, prenatal alcohol and tobacco use, medical history, maternal IQ, HOME score, family income, language spoken at home, parental education
			Language: preschool language scale scores weakly and <i>positively</i> associated with current child and prenatal maternal hair mercury levels; regression coefficients and std errors	child hair 0.18±0.08 maternal prenatal hair 0.13±0.06	+ +	As above
			Visual-spatial function: errors on Bender Gestalt test <i>inversely</i> associated with current child but not prenatal maternal hair mercury levels; regression coefficients and std errors	child hair -0.16 ±0.06 maternal prenatal hair 0.04±0.05	+	As above
			Reading and arithmetic scores <i>positively</i> associated with current child but not prenatal maternal hair mercury levels; regression coefficients and std	child hair 0.36 ±0.18 maternal prenatal hair	+	As above

			errors	0.11±0.14		
(Myers and Davidson 1998)	Literature review		Prenatal maternal consumption of marine fish from non-industrially polluted regions does not cause adverse neurodevelopmental outcomes			
(Altmann et al. 1998), 3 areas of Germany	Cross-sectional study, 384 children age 5-7 yr; measured visual evoked potentials	GM 24-hr urinary mercury 0.16 (range 0.02-2.83 µg)	Visual contrast sensitivity at certain spatial frequencies inversely associated with urinary mercury among children age 5-7 yr; β -coefficients for contrast sensitivity at 3 cycles per degree	left eye $\beta=-0.12$, $p=0.04$ right eye $\beta=-0.14$, $p=0.03$	+	Area, age, lactation duration, study area, head circumference, visual acuity, parental education
			Visual-evoked potential indices not associated with urinary mercury among children age 5-7 yr (result stated without supporting data in paper)			
(Counter et al. 1998), Ecuador	Cross-sectional study, 36 children age 3-15 yr in gold mining region and 15 in comparison village; conducted neurologic examination, audiometry (21 children) and auditory brainstem response tests (19 children)	Mean blood mercury in exposed and unexposed children were 16.2 (range 6-45 µg/L) and 2.4 (range 1.0-6.0 µg/L)	Hearing threshold at 3 kHz in right ear but not in left ear among children age 3-15 yr inversely associated with current blood mercury; Pearson correlation coefficient	$r=0.55$, $p=0.01$	+	
			I-III auditory brainstem evoked potential interval on left but not on right side associated with current blood mercury among children age 3-15 yr	$r=0.45$, $p=0.05$	+	

(Mahaffey 1999)	Summary of 1997 Mercury Study Report to Congress		Methylmercury is a human neurotoxin with prominent sensorimotor effects; the fetal nervous system is the most sensitive organ system			
			Prenatal maternal hair mercury levels of 3-10 $\mu\text{g/g}$ associated with language, attention and memory deficits among Faroese children			
			There is a steep dose-response relationship between methylmercury and neurotoxicity in experimental animals; subclinical toxicity occurs at 1.1 $\mu\text{g/g}$ in diet, ataxia at 1.8 $\mu\text{g/g}$ and death at 4.8 $\mu\text{g/g}$			
(Grandjean et al. 1999b), Faroe Islands	Birth cohort study, 917 children age 7 yr; compared associations between neuropsychologic test results and methylmercury exposure indices	GM mercury in cord blood 23 $\mu\text{g/L}$, prenatal maternal hair 4.3 $\mu\text{g/g}$, child hair at ages 1 yr (1.1 $\mu\text{g/g}$) and 7 yr (3.0 $\mu\text{g/g}$), child blood at age 7 yr 8.8 $\mu\text{g/L}$	Motor function: finger tapping (preferred hand) speed at age 7 yr inversely associated with prenatal but not postnatal exposure indices; score change as percent of standard deviation per doubling of mercury concentration	cord blood -5.4, $p=0.05$ prenatal maternal hair -6.0, $p=0.04$ hair 1 yr -1.0, $p=0.82$ hair 7 yr -0.6, $p=0.79$ blood 7 yr 3.5, $p=0.23$	+	Age, sex, maternal IQ, obstetric risk factors, daycare, parental education, paternal employment; included duration of breastfeeding in analyses of child hair mercury

		Associations between neuropsychologic deficits and mercury exposure indices generally strongest for cord blood	Attention: CPT reaction time at age 7 yr associated with prenatal and infant but not later childhood exposure indices; score change as percent of standard deviation per doubling of mercury concentration	cord blood 16, p<0.001 prenatal maternal hair 9.0, p=0.04 hair 1 yr 12, p=0.05 hair 7 yr 5.1, p=0.16 blood 7 yr 6.5, p=0.12	+	As above
			Attention: WISC digit span scores at age 7 yr inversely associated with cord blood but not other exposure indices; score change as percent of standard deviation per doubling of mercury concentration	cord blood -5.6, p=0.05 prenatal maternal hair -4.4, p=0.15 hair 1 yr 0.9, p=0.83 hair 7 yr 2.3, p=0.34 blood 7 yr 2.4, p=0.43	+	As above
			Cognitive function: WISC similarities and block design scores at age 7 yr not associated with any mercury			As above

			exposure index			
			Visuospatial function: errors on visual Bender Gestalt test at age 7 yr not associated with any mercury exposure index			As above
			Language: Boston naming test scores at age 7 yr inversely associated with prenatal but not postnatal exposure indices; score change as percent of standard deviation per doubling of mercury concentration	cord blood -9.8, p<0.001 prenatal maternal hair -7.0, p=0.02 hair 1 yr 2.9, p=0.05 hair 7 yr -1.0, p=0.66 blood 7 yr -3.5, p=0.23	+	As above
			Memory: California verbal learning long-term memory scores at age 7 yr inversely associated with cord blood but not other exposure indices; score change as percent of standard deviation per doubling of mercury concentration	cord blood -5.7, p=0.05 prenatal maternal hair -5.2, p=0.09 hair 1 yr 4.1, p=0.34 hair 7 yr -1.2, p=0.63 blood 7 yr	+	As above

				-1.4, p=0.65		
(Grandjean et al. 1999a), Amazon basin	Cross-sectional study, 351 children age 7-12 yr from 3 villages downstream from gold mining region and a comparison village; conducted tests of finger tapping speed, motor coordination and dexterity (Santa Ana form board), attention and information processing (WISC-III digit spans test) and visuospatial function and nonverbal memory (copying and bead memory tests from Stanford-Binet Intelligence Scale)	Maternal and child hair GM mercury levels were 11.6 and 11.0 µg/g; hair mercury levels above 10 µg/g occurred in over 80% of children from 3 exposed villages and in 2% of those from comparison village; strong correlation between maternal and child hair mercury levels (r=0.80 after log transformation)	Motor function: finger tapping speed and dexterity (preferred hand) among children age 7-12 yr inversely associated with current hair mercury levels	finger tapping β=-6.5, p<0.001 dexterity β=-2.2, p=0.005	+	Adjustment for age, sex, maternal education and marital status had little influence; only age and sex included in final analyses; villages all had low SES and low prevalence of maternal alcohol use
			Attention/information processing: WISC digit span scores among children age 7-12 yr inversely associated with current hair mercury levels	β=-0.9, p=0.001	+	As above
			Cognitive function: Stanford-Binet subscale scores for visuospatial/visuoconstructional and memory functions among children age 7-12 yr inversely associated with current hair mercury levels	visuospatial β=-6.2, p<0.001 bead memory β=-2.9, p<0.001	+	As above
(Murata et al. 1999b), Faroe Islands	Cross-sectional study; remeasured auditory brainstem evoked potentials	GM mercury in cord blood 23 (range 3.3-351 µg/L), prenatal maternal	III brainstem auditory evoked potential latencies at 20 and 40 Hz associated with cord blood	cord blood β=0.11, p=0.02	+	Age, sex, maternal IQ, obstetric and postnatal risk factors,

	using new equipment	hair 4.5 (range 0.6-39 $\mu\text{g/g}$), child hair at age 7 yr 3.4 (range 0.04-26 $\mu\text{g/g}$)	and prenatal maternal hair but not current child hair mercury levels; β -coefficients for III latency at 40 Hz	mat hair $\beta=0.12$, $p=0.01$ child hair $\beta=0.02$, $p=0.68$	+	daycare, parental education, paternal employment
			I-III brainstem auditory evoked potential intervals at 20 Hz associated with cord blood and prenatal maternal hair but not current child hair mercury levels; β -coefficients for 20 Hz shown; no associations at 40 Hz	cord blood $\beta=0.10$, $p=0.04$ mat hair $\beta=0.10$, $p=0.04$ child hair $\beta=0.01$, $p=0.83$	+	As above
(Murata et al. 1999a), fishing community, Madeira	Cross-sectional study, 149 children age 6-7 yr; measured brainstem auditory and pattern-reversal visual evoked potentials	GM current hair mercury 3.8 $\mu\text{g/g}$ (range 0.4-26); GM prenatal maternal hair mercury 9.6 $\mu\text{g/g}$ (range 1.1-54)	I-III brainstem auditory evoked potential interval at 40 Hz among children age 7 yr associated with prenatal maternal but not current child hair mercury levels	child hair $\beta=0.10$, $p=0.14$ prenatal maternal hair $\beta=0.22$, $p=0.002$	+	Age, sex
			Brainstem visual evoked potential latencies among children age 7 yr not associated with prenatal maternal or current child hair mercury levels; results for P100-N145 latencies shown	child hair $\beta=3.5$, $p=0.17$ prenatal maternal hair $\beta=4.0$, $p=0.09$		As above
(Axtell et al. 2000), Seychelles Islands	Birth cohort study, 711 children age 5-6 yr; assessed non-linearity of associations between neuropsychologic tests and prenatal and postnatal	Mean prenatal maternal hair mercury 6.8 (range 0.5-27 $\mu\text{g/g}$); mean current child hair mercury 6.5 (range 0.9-26 $\mu\text{g/g}$); few persons had hair	Language (Preschool Language Scale) and social/adaptive behaviour (Child Behavior Checklist) scores at age 5-6 yr appeared to increase with prenatal maternal hair mercury	language $p=0.10$ social/adaptive behaviour $p=0.05$	+	Sex, birth weight, birth order, breastfeeding, IUGR, hearing score, HOME score, SES, maternal age,

	methylmercury exposure indices; used generalized additive models (GAMs)	mercury above 10 µg/g, causing imprecise risk estimates in this range	concentrations up to 10 µg/g and then decrease (p for non-linearity)			toxemia, maternal IQ, prenatal maternal smoking and alcohol; note – included both maternal and child hair mercury levels in analyses
			McCarthy general cognitive index at age 5-6 yr appeared to increase with current child hair mercury concentrations up to 10 µg/g and then decrease (p for non-linearity)	p=0.04	+	As above
(Palumbo et al. 2000), Seychelles Islands	Birth cohort study, 711 children age 5-6 yr; recombined 18 McCarthy subtests into groups for attention, executive functions (mental flexibility and conceptual reasoning), expressive language, language comprehension, nonverbal memory, verbal memory, visuospatial organization (ability to integrate and respond to complex visual stimuli), visuomotor integration (copying/drawing skills), gross motor coordination	Mean prenatal maternal hair mercury 6.8 µg/g (range 0.5-27); mean current child hair mercury 6.5 µg/g (range 0.9-26)	No adverse associations between the standard McCarthy subscale scores at age 5-6 yr and prenatal maternal or current child hair mercury levels; regression coefficients for maternal prenatal hair shown (test point change per µg/g hair mercury)	verbal -0.06±0.07 performance -0.09±0.08 memory 0.02±0.07 quantitative 0.10±0.06 motor -0.12±0.08		Sex, birth weight, birth order, breastfeeding, IUGR, hearing score, HOME score, SES, maternal age, toxemia, maternal IQ, prenatal maternal smoking and alcohol, language spoken in home
			No adverse associations between the recombined McCarthy subscale scores at age 5-6 yr and prenatal maternal or current child hair	executive function -0.006±0.008 expressive		As above

			mercury levels; regression coefficients for maternal prenatal hair shown (test point change per $\mu\text{g/g}$ hair mercury)	language -0.003 \pm 0.008 verbal memory 0.007 \pm 0.008 nonverbal memory -0.014 \pm 0.008 visuomotor -0.009 \pm 0.009 attention 0.012 \pm 0.008		
(Davidson et al. 2000), Seychelles Islands	Cohort study, follow-up at age 9 yr of 87 children recruited in previous cross-sectional study; conducted 5 of 13 WISC-III subtests, California Verbal Learning Test, Boston Naming Test and tests of visual-motor integration, design memory, manual dexterity and finger tapping speed	Median prenatal maternal hair mercury 7.8 $\mu\text{g/g}$ (range 0.6-35)	Cognitive function: WISC-III subtest scores at age 9 yr not associated with prenatal maternal hair mercury; regression coefficients \pm SE	block design 0.02 \pm 0.05 coding -0.05 \pm 0.05 information -0.02 \pm 0.03 vocabulary 0.004 \pm 0.03		Child – sex, post-enrollment disability; mother – age, prenatal alcohol and tobacco use, SES, family crises
			Motor function: grooved pegboard time (preferred hand) at age 9 yr inversely associated (favourable outcome) with prenatal maternal hair mercury; regression coefficients \pm SE	-1.07 \pm 0.045	+	As above
			Visual motor integration score associated (favourable	0.62 \pm 0.27	+	As above

			outcome) with prenatal maternal hair mercury; regression coefficients±SE		
(Myers et al. 2000b), Seychelles Islands	Birth cohort study, 711 children age 5-6 yr; conducted Achenbach Child Behavior Checklist (CBCL)	Mean prenatal maternal hair mercury 6.8 µg/g (range 0.5-27); mean current child hair mercury 6.5 µg/g (range 0.9-26)	Inattention, aggressive and other behaviours not associated with prenatal maternal or current child hair mercury levels; regression coefficients+SE shown for selected outcomes vs prenatal maternal hair mercury	inattention -0.045±0.06 aggressive behaviour -0.002±0.001	Sex, birth weight, IUGR, maternal age, HOME score, SES, maternal IQ, hearing acuity
(Budtz-Jorgensen et al. 2000), Faroe Islands	Birth cohort study, 917 children age 6-7 yr; estimated benchmark doses for association between cord blood mercury and fine motor function (finger tapping speed), attention (continuous performance test), visuospatial performance (Bender Visual Motor Gestalt test), language (Boston naming test) and verbal memory (California Verbal Learning test)	Cord blood and prenatal maternal hair mercury	BMDLs for prenatal maternal hair mercury levels (based on a logarithmic dose-response model and a 5% probability of an adverse response)	finger tapping speed 4.3 µg/g attention 2.2 µg/g visual-spatial 6.8 µg/g language 3.0 µg/g verbal memory 4.8 µg/g	Age, sex, maternal IQ, and, as necessary, IUGR, daycare, parental education, paternal employment
			BMDLs for cord blood mercury level (based on a logarithmic dose-response model and a 5% probability of an adverse response)	finger tapping speed 7.9 µg/L attention 1.6 µg/L visual-spatial	As above

				13 µg/L language 3.1 µg/L verbal memory 7.6 µg/L	
(Myers et al. 2000a; Myers and Davidson 2000)	Literature reviews	Methylmercury exposure during pregnancy and early childhood	Limited evidence that low-level exposure (prenatal maternal hair mercury about 10 µg/g) can cause developmental disabilities; no evidence that exposure to methylmercury from fish alone causes neurobehavioural deficits		
(Stewart et al. 2000), Oswego Newborn and Infant Development Project, New York State	Birth cohort study, 141 neonates of women exposed to Lake Ontario fish and 152 neonates of unexposed women; conducted Neonatal Behavioral Assessment Scale (NBAS) twice (on postnatal days 1 and 2)	Assessed maternal fish consumption; measured prenatal maternal hair mercury during late gestation; 75 th percentile was 0.7 µg/g	NBAS subscale scores not associated with prenatal maternal hair mercury levels	habituation β=-0.09, p=0.15 autonomic β=-0.08, p=0.21 reflexes β=-0.02, p=0.76	HOME scores, parental education, SES, paternal age, prepregnancy weight, weight gain during pregnancy, stress during early gestation, smoking, ETS, caffeine, prenatal vitamin and prescription drug use, child sex, birth weight, head circumference
(Darvill et al. 2000), Oswego Newborn and Infant Development	Birth cohort study, offspring of women consuming Lake Ontario fish; examined 230 infants at 6 mos and 216 at 12 mos using the Fagan Test	See Stewart et al 2000 above; median contaminant levels were cord blood total PCBs (0.5 µg/L) and lead (2.0	No association between Fagan test scores at 6 or 12 mos and prenatal maternal hair mercury levels; correlation coefficient	6 mos r=0.10, p=0.14 12 mos r=.05, p=0.42	

Project, New York State	of Infant Intelligence (a test of preference for a novel stimulus – the latter implies intact short term memory)	µg/dL), breast milk total PCBs (153 ng/g lipid) and prenatal maternal hair mercury (0.5 µg/g)				
(Crump et al. 2000)	Seychelles birth cohort study; estimated benchmark dose lower limits (BMDLs) based on the lower 95% confidence limit of prenatal maternal hair mercury levels corresponding to a 10% probability of adverse neuropsychologic test scores conducted at ages 6, 19, 29 and 66 mos	Prenatal maternal hair mercury (mean 6.8, range 0.5-27 µg/g)	BMDLs at age 6 mos	visual recognition memory 26 µg/g attention 26 µg/g		Inclusion of covariates had little influence on BMDL estimates
			BMDLs at age 5.5 yr	McCarthy general cognitive index 24 µg/g visual-motor function 27 µg/g language 25 µg/g		
(National Academy of Sciences 2000)	Literature review		Chronic low-level prenatal methylmercury exposure from maternal fish consumption was associated with subtle neuropsychologic deficits including attention, fine-motor function, language, visual-spatial abilities and verbal memory in two of three large			

			epidemiologic studies			
			Animal studies show that the developing nervous system is sensitive to cognitive, motor and sensory deficits from low-dose methylmercury exposure			
(Grandjean et al. 2001b), Faroe Islands	Birth cohort study, 435 children age 7 yr; conducted Neurobehavioral Evaluation System, hand-eye coordination, continuous performance, WISC-R digit spans, similarities and block design subtests, Bender Gestalt visual-motor, California Verbal Learning, Boston Naming	Cord tissue PCB levels (median 1.0 $\mu\text{g/g}$ lipid), DDE (median 0.7 $\mu\text{g/g}$ lipid), cord blood mercury (median 26 $\mu\text{g/L}$), neonatal blood TSH and T4 levels	Motor function: borderline inverse association between finger tapping speed (preferred hand) at age 7 yr and cord blood mercury; borderline association between hand-eye coordination errors at age 7 yr and cord blood mercury	finger tapping $\beta=-1.6$, $p=0.08$ hand-eye coordination $\beta=0.065$, $p=0.10$	(+)	Age, sex, and, as necessary, maternal IQ, IUGR, parental education and employment, day care, computer acquaintance
			Attention: CPT reaction time and WISC digit span score at age 7 yr associated with cord blood mercury	reaction time $\beta=40.3$, $p=0.0002$ digit span $\beta=-0.52$, $p=0.02$	+ +	As above
			Cognitive function: WISC similarities and block design scores at age 7 yr not associated with cord blood mercury	similarities $\beta=-0.57$, $p=0.35$ block design $\beta=-0.13$, $p=0.43$		As above
			Visual-motor function: Bender Gestalt errors at age 7 yr not	$\beta=1.26$, $p=0.11$		As above

			associated with cord blood mercury			
			Language: Boston Naming test scores at age 7 yr inversely associated with cord blood mercury	$\beta=-1.49$, $p=0.05$	+	As above
			Memory: California Verbal Learning test scores at age 7 yr inversely associated with cord blood mercury	$\beta=-0.94$, $p=0.04$	+	As above
(Grandjean et al. 2001a), Faroe Islands	Birth cohort study, 435 children age 7 yr; reassessed neuropsychologic test scores among children with normal vision (no strabismus, not using glasses) and with adjustment for contrast sensitivity	Cord tissue PCB levels (median 1.0 $\mu\text{g/g}$ lipid), DDE (median 0.7 $\mu\text{g/g}$ lipid), cord blood mercury (median 26 $\mu\text{g/L}$), neonatal blood TSH and T4 levels	Cognitive function: WISC block design and similarities scores not associated with cord blood mercury among children age 7 yr (restricted to those with normal vision)	block design $\beta=-0.12$, $p=0.25$ similarities $\beta=-0.08$, $p=0.84$		Age, sex, and, as necessary, maternal IQ, IUGR, parental education and employment, day care, computer acquaintance, visual contrast sensitivity
			Attention: WISC digit span and CPT reaction time associated with cord blood mercury among children age 7 yr (restricted to those with normal vision)	digit span $\beta=-0.27$, $p=0.06$ reaction time $\beta=37.6$, $p=0.001$	(+) +	
			Motor function: inverse association between finger tapping speed (preferred hand) but not hand-eye coordination errors and cord blood mercury among children age 7 yr (restricted to those with normal	finger tapping $\beta=-1.29$, $p=0.03$ hand-eye coord $\beta=0.01$, $p=0.71$	+	

			vision)			
			Visual motor function: Bender Gestalt copying errors not associated with cord blood mercury among children age 7 yr (restricted to those with normal vision)	$\beta=0.52$, $p=0.28$		
(Clarkson 2002)	Literature review		Body of evidence supports association between developmental milestone delays during infancy and prenatal maternal hair mercury levels as low as 10 $\mu\text{g/g}$			
(United Nations Environment Programme, 2002)	Literature review		Some evidence that low-level prenatal methylmercury exposure can cause neurotoxic effects (attention, verbal memory and language deficits)			
(Newland 2002)	Literature review		Gestational or lactational exposure affects high-order visual functions (contrast sensitivity, pattern recognition), motor deficits (nystagmus, cerebral palsy)			
			Methylmercury affects the visual, auditory and somatosensory systems at the cortical level; visual effects are strongly age-dependent			
(Weihe et al. 2002), Thule,	Cross-sectional study, 43 Inuit children age 7-12 yr;	Cord blood mercury, current child and prenatal	Non-significant association between CPT reaction time and	$r_s=0.34$, $p=0.13$		

Greenland	conducted neurologic examination, finger tapping test, hand-eye coordination test, continuous performance test (CPT), WISC subscales for digit spans and block designs, Stanford-Binet memory test; pooled data for 629 Inuit, Madeira and Faroe Islands children for assessment of brainstem auditory- and visual-evoked potential latencies	maternal hair mercury	log cord blood mercury (Pearson r)			
			Hand-eye coordination test errors associated with log prenatal maternal hair mercury (Pearson r)	$r_s=0.44, p=0.01$	+	
			Brainstem auditory-evoked potential latencies associated with log prenatal maternal hair mercury; latencies at 40 Hz (multiple regression coefficients)	I-III 0.11, $p<0.05$ I-V 0.08, $p<0.05$	+	+
			Brainstem visual-evoked potential latencies not associated with log prenatal maternal hair mercury; N145 latencies at 30' (multiple regression coefficient)	-2.2, $p>0.05$		
(Cordier et al. 2002), French Guiana	Cross-section study, 378 Amerindian children age 9 mos to 6 yr; from communities with high,	Exposure from contaminated fresh-water fish in gold mining regions; measured	Finger tapping and leg coordination test scores not associated with mother's hair mercury level	finger tapping $\beta=-1.6, p=0.44$ leg		Age, sex, examiner, parity

	intermediate or low methylmercury exposure levels, recruited during 1997-1998; conducted neurological examination, finger tapping test, McCarthy leg coordination and digit span tests, Stanford-Binet copying and bead memory tests	mercury in hair from children and their mothers; GM 12.7 $\mu\text{g/g}$		coordination $\beta=-0.15$, $p=0.62$		
			Scores on Stanford-Binet copying test of visuospatial organization not associated with mother's hair mercury level	$\beta=-3.0$, $p<0.001$	+	Age, sex, examiner, place of birth
			Scores on Stanford-Binet bead memory test not associated with mother's hair mercury level	$\beta=0.1$, $p=0.92$		Age, sex, examiner
(Murata et al. 2002)	Benchmark dose estimation for auditory-evoked potential latencies using data from the Faroe Islands (n=382) and Madeira (n=113) studies; children were age 7 yr and were free of middle ear infection or neurologic disease	Prenatal maternal hair mercury levels in Faroe Islands were 0.6-39.1 $\mu\text{g/g}$ (geometric mean 4.5 $\mu\text{g/g}$) and in Madeira were 1.1-54 $\mu\text{g/g}$ (geometric mean 10.1 $\mu\text{g/g}$)	Latencies for auditory-invoked potentials at 20 and 40 Hz were associated with prenatal maternal hair mercury in both groups			
			The benchmark dose for a doubling of a 5% prevalence of abnormal latencies at 40 Hz was 9.5 $\mu\text{g/g}$ for both groups combined; similar results at 20 Hz			

(Grandjean et al. 2003a), Faroe Islands	Birth cohort, 596 children age 7 yr (restricted to children for whom mercury levels in two prenatal maternal hair segments were available); conducted neuropsychologic tests (finger tapping, hand-eye coordination, continuous performance, WISC-R, Bender Visual Motor Gestalt, Boston Naming, California Verbal Learning tests)	Measured mercury in cord blood and two maternal hair segments corresponding to total and late gestation	Among children with consistent prenatal maternal hair mercury levels, scores on all 16 neuropsychologic tests were inversely associated with cord blood mercury levels (results for 10 tests were statistically significant); neuropsychologic test scores more closely associated with cord blood than with prenatal maternal hair mercury levels			Age, sex, medical risk factors, maternal IQ, daycare, parental education, paternal employment
		After excluding 61 children with discrepancies between two prenatal maternal hair mercury levels, the associations between cord blood mercury and verbal learning and memory deficits persisted and were slightly stronger	Attention: WISC digit span and CPT reaction time associated with cord blood mercury among children age 7 yr (restricted to those with stable duplicate prenatal maternal hair mercury levels)	digit span $\beta=-0.32$, $p=0.10$ reaction time $\beta=47.0$, $p<0.001$	+	As above
			Motor function: unfavourable associations between finger tapping speed (preferred hand) and hand-eye coordination errors and cord blood mercury among children age 7 yr (restricted to those with stable duplicate prenatal maternal hair mercury levels)	finger tapping $\beta=-1.45$, $p=0.05$ hand-eye coord $\beta=0.076$, $p<0.03$	+ +	As above
			Cognitive function: borderline inverse association between	$\beta=-0.28$, $p=0.06$	(+)	As above

			WISC block design scores and cord blood mercury among children age 7 yr (restricted to those with stable duplicate prenatal maternal hair mercury levels)			
			Visual motor function: Bender Gestalt copying errors associated with cord blood mercury among children age 7 yr (restricted to those with stable duplicate prenatal maternal hair mercury levels)	$\beta=1.53, p<0.03$	+	As above
			Language: Boston Naming Test scores inversely associated with cord blood mercury among children age 7 yr (restricted to those with stable duplicate prenatal maternal hair mercury levels)	$\beta=-1.59, p<0.02$	+	As above
			Memory: California Verbal Learning Test long-term recall scores inversely associated with cord blood mercury among children age 7 yr (restricted to those with stable duplicate prenatal maternal hair mercury levels)	$\beta=-0.81, p<0.04$	+	As above
(Myers et al. 2003), Seychelles Islands	Longitudinal cohort study, 643 infants enrolled during 1989-1990 and followed to age 9 yr; assessed neurocognitive, language,	Mothers consumed fish avg 12 meals/wk; measured prenatal maternal hair mercury and child hair mercury in	WISC III full-scale IQ not associated with maternal prenatal hair mercury levels	$\beta=-0.13, p=0.20$		Child age, sex, medical history, maternal age, HOME score, caregiver intelligence, SES,

	memory, motor, perceptual-motor and behavioural functions	segment representing previous month				hearing (better ear), child's mercury level, examiner, family resource scale, family status code, HELPS score
			CVLT verbal memory, BNT language and W-J applied problem test scores at age 9 yrs not associated with maternal prenatal hair mercury levels; selected results shown	Calif Verbal Learning Test 0.01, p=0.28 Boston Naming Test -0.01, p=0.79 Woodcock-Johnson test -0.06, p=0.71		As above
			Various motor function test scores not associated with maternal prenatal hair mercury levels; selected results shown: visual-motor integration, Bruninks-Oseretsky, finger tapping (dominant hand)	VMI -0.01, p=0.93 motor efficiency 0.09, p=0.10 fine motor fcn -0.05, p=0.34		
			Attention and behaviour scores not associated with maternal prenatal hair mercury levels (except for hyperactivity score where a there was a favourable association); selected results shown – continuous performance task attentiveness,	CPT attentiveness -0.006, p=0.95 problem behaviours -0.03, p=0.10		

			Connor's child problem behaviour checklist, Connor's teacher-rated hyperactivity	hyperactivity -0.007, p=0.002	+	
(Counter 2003), Ecuador	Cross-sectional study, 31 children age 4-14 yr from Andean gold mining village, less exposed comparison group of 21 children; measured brainstem auditory evoked potentials	Current blood mercury level; range in gold mining village was 2-89 µg/L (mean 23.0), range in comparison village was 1-10 µg/L (mean 4.5)	Brainstem auditory evoked potential wave V latency and I-V interval were associated with current blood mercury level; Spearman correlation coefficients	V latency $r_s=0.38$, $p=0.03$ I-V interval $r_s=0.41$, $p=0.02$	+	
(Daniels et al. 2004), ALSPAC study, UK	Longitudinal cohort study, 7421 children born in 1991-1992; conducted MacArthur Communicative Development Inventory (MCDI) at 15 mos and the Denver Developmental Screening Test (DDST) at age 18 mos	Self-reported maternal fish intake; measured cord tissue mercury in a subset of 1054 children	MCDI scores at age 15 mos not associated with umbilical cord tissue mercury levels; β trend (change in odds of high developmental score points per ounce increase of maternal fish per wk)	vocabulary comprehension 6.1, $p=0.8$ social activity -0.2, $p=0.9$		Child's age at testing, sex, birth order, fish intake, breastfeeding status, maternal fish intake, age, education, dental treatment, smoking, alcohol, HOME score
			DDST scores at age 18 mos not associated with umbilical cord tissue mercury levels; β trend	language 0.1, $p=0.9$ social activity 0.5, $p=0.8$		As above
			Verbal comprehension, social activity and language scores at age 15 mos positively associated with maternal prenatal fish intake frequency; β trend	<i>age 15 mos</i> verbal comprehension 0.01, $p=0.05$ social activity 0.02, $p=0.02$ <i>age 18 mos</i>	+	Fish intake at other times, child's age at testing, sex, birth order, breastfeeding status, maternal age, education, dental treatment, smoking, alcohol, HOME score

				language 0.006, p=0.03		
				social activity -0.001, p=0.9		
(Davidson et al. 2004), USA	Review of epidemiologic studies of mercury exposure and child development outcomes	Mercury levels in prenatal maternal hair segments corresponding to pregnancy: Iraq (1-600 ppm), Seychelles Islands (≤ 36 ppm)	Iraq – the dose-response relationship between delayed developmental milestones and prenatal maternal hair mercury level indicated adverse effects at levels as low as 10-20 ppm			
			Results of small studies in Peru, Canada, New Zealand, the Philippines, Brazil and French Guinea vary and show no consistent pattern of adverse effects			
		Exposure source: daily fish consumption; fish contained methylmercury but not PCBs; used prenatal maternal hair as only biomarker of exposure	Seychelles Islands – among 46 outcomes, only one was associated with prenatal methylmercury exposure (time to complete grooved pegboard using non-preferred hand, boys age 9 yr); two favourable associations with prenatal methylmercury exposure were language function at age 5.5 yr and teacher-rated ADHD index at age 9 yr			
		Exposure source: intermittent consumption of pilot whale containing methylmercury and	Faroe Islands – found associations between prenatal methylmercury exposure and tests of memory, attention,			

		PCBs; used cord blood and prenatal maternal hair mercury as exposure biomarkers	language and visual spatial perception at age 7 yr			
			Noted absence of any human data on health effects of prenatal or early postnatal exposure to elemental or inorganic mercury			
(Murata et al. 2004), Faroe Islands	Longitudinal cohort study, 878 children recruited during 1986-1987 and followed to age 14 yr; assessed latencies of brainstem auditory-evoked potential peaks I, III and V at 20 and 40 Hz	Measured mercury in cord blood, prenatal maternal hair, child's hair at ages 7 and 14 yr	Wave III and V and I-III interpeak latencies at 20 Hz associated with cord and prenatal maternal hair mercury but not child hair mercury at age 7 or 14 yr; regression coefficients for wave III latency vs log mercury concentration; similar results for wave V and I-III interpeak latencies	Cord blood 0.045, p=0.002 Mat hair 0.037, p=0.01 Hair age 7 0.012, p=0.34 Hair age 14 0.001, p=0.91	+	Sex, age; note – brainstem auditory-evoked potential latencies appear to be independent of SES

Neuropsychologic deficits summary

Cognitive function among preschool-age children

Low-level prenatal methylmercury exposure The Seychelles Islands birth cohort study found no associations between the Denver Developmental Screening Test scores, Bayley Scales of Infant Development or Fagan visual recognition and visual attention scores among infants age 6-29 months and prenatal maternal hair mercury levels (Myers et al 1995b, Davidson et al 1995). Using data from the latter study on Fagan tests of visual recognition memory and attention at age 6 months, the estimated average benchmark dose lower limit (BMDL) for a 10% probability of an adverse outcome was 26 µg/g for prenatal maternal hair (Crump et al 2000). A small birth cohort study among women who consumed Lake Ontario fish found no associations between Neonatal Behavioral Assessment Scale scores or Fagan Test of Infant Intelligence scores at ages 6 or 12 months and prenatal maternal hair mercury levels (Stewart et al 2000, Darvill et al 2000). A UK birth cohort study found no associations between MacArthur Communicative Development Inventory scores at age 15 months or Denver Developmental Screening Test scores at age 18 months and umbilical cord tissue mercury levels (Daniels et al 2004).

Cognitive function among school-age children

Low-level prenatal methylmercury exposure Literature reviews by Grandjean et al (1994, 1996) concluded that full-scale IQ deficits are associated with prenatal maternal hair mercury levels above 15 µg/g. In the Seychelles Islands pilot study, the McCarthy general cognitive index among children age 5 years was

inversely associated with prenatal maternal hair mercury levels; after removal of outliers, these associations were not statistically significant (Myers et al 1995a). Follow-up of children in the latter study showed no associations between WISC-III subscale scores at age 9 years and prenatal maternal hair mercury levels (Davidson et al 2000). The Seychelles Islands birth cohort main study found no associations between full-scale IQ or subscale scores at ages 5 or 9 years and maternal or child hair mercury levels (Davidson et al 1998, Axtell et al 2000, Palumbo et al 2000, Myers et al 2003). Based on McCarthy general cognitive index values at age 5 years in the Seychelles Islands birth cohort study, the estimated benchmark dose lower limit (BMDL) for a 10% probability of an adverse outcomes was 24 $\mu\text{g/g}$ for prenatal maternal hair (Crump et al 2000). Results from generalized additive model analysis of the Seychelles Islands cohort data suggested a nonlinear dose-response relationship whereby McCarthy general cognitive index scores at age 5-6 years increased with prenatal maternal hair mercury concentrations up to 10 $\mu\text{g/g}$ and then decreased (Axtell et al 2000). Literature reviews by Myers and colleagues concluded that there is limited evidence that low-level prenatal methylmercury exposure can cause developmental disabilities and no evidence that exposure to methylmercury from fish alone causes neurobehavioural deficits (Myers et al 2000a, Myers and Davidson 1998, 2000).

In the Faroe Islands birth cohort study there were no associations between WISC similarity and block design subscale scores at age 7 years and prenatal maternal hair, cord blood or current child hair or blood mercury levels (Grandjean et al 1997, 1999b, 2001b). Reanalyses of the Faroe Islands birth cohort study showed that: (i) after excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, there were no associations between WISC subscale scores at age 7 years and cord blood mercury levels (Grandjean et al 2001a), and, (ii) restriction to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, there was a borderline inverse association between WISC block design scores at age 7 years and cord blood mercury levels (Grandjean et al 2003). A reanalysis of a New Zealand birth cohort study found a borderline inverse association between McCarthy general cognitive index scores at ages 6-7 years and prenatal maternal hair mercury levels (after excluding the child with the highest prenatal maternal hair mercury level) (Crump et al 1998).

Expert panel reviews noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with language, verbal memory and other subtle neuropsychologic deficits in two large epidemiologic studies and experimental animal evidence for cognitive, motor and sensory deficits at low prenatal methylmercury exposure levels (National Academy of Sciences 2000, United Nations Environment Programme 2002). A recent literature review noted that among 46 neuropsychologic outcomes measured in the Seychelles Islands birth cohort study: (i) only one was unfavourably associated with prenatal methylmercury exposure, i.e., time to complete the grooved pegboard test using the non-preferred hand, boys age 9 years, and, (ii) there were two favourable associations with prenatal maternal hair mercury levels, i.e., language function at age 5 years and teacher-rated ADHD index at age 9 years (Davidson et al 2004). The latter review also noted that the Faroe Islands birth cohort study found associations between prenatal maternal hair and/or cord blood mercury levels and tests of memory, attention, language and visual spatial perception at age 7 years.

Low-level postnatal methylmercury exposure indices A cross-sectional study of children age 5-7 years in the former East Germany found no association between WISC block design subtest scores and current urinary mercury levels (Walkowiak et al 1998). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found inverse associations between Stanford-Binet subscale scores for visuospatial/visuoconstructional and memory functions among children age 7-12 years and current child hair mercury levels (Grandjean et al 1999a).

Language

Low-level prenatal methylmercury exposure In the Seychelles Islands birth cohort study, language performance scores at ages 5-6 years were weakly and *positively* associated with prenatal maternal hair mercury levels (Davidson et al 1998). Results from generalized additive model analysis of the Seychelles

Islands cohort data suggested a nonlinear dose-response relationship whereby language scores at age 5-6 years increased with prenatal maternal hair mercury concentrations up to 10 µg/g and then decreased (Axtell et al 2000). Using continuous values of language scores at age 5 years in the Seychelles Islands birth cohort study, the estimated benchmark dose lower limit (BMDL) for a 10% probability of an adverse outcomes was 25 µg/g for prenatal maternal hair mercury (Crump et al 2000). Language test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). In the Faroe Islands birth cohort study, language scores (Boston Naming Test) were inversely associated with prenatal maternal hair and cord blood mercury levels (Grandjean et al 1997, 1998, 1999b, 2001b). The association between language scores and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). However, the association was weaker and statistically non-significant after inclusion of umbilical cord tissue PCB levels in the analytic model (Grandjean et al 1997). Data from the Faroe Islands birth cohort study on language scores at age 7 years yielded a BMDL of 3.0 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found that language scores (Boston Naming Test) at age 7 years were inversely associated with cord blood mercury levels (Grandjean et al 2003). A literature review by the United Nations Environment Programme (2002) concluded that there is some evidence that low-level prenatal methylmercury exposure can cause language deficits. A UK birth cohort study showed that verbal comprehension scores at age 15 months and language test scores at age 18 months were not associated with umbilical cord tissue mercury levels but were favourably associated with maternal prenatal fish intake frequency (Daniels et al 2004).

Low-level prenatal methylmercury exposure In the Seychelles Islands birth cohort study, language performance scores at ages 5-6 years were weakly and *positively* associated with current child hair mercury levels (Davidson et al 1998). In the Faroe Islands birth cohort study, language scores (Boston Naming Test) were not associated with current child hair or blood mercury levels (Grandjean et al 1997, 1998, 1999b, 2001b). A cross-sectional study in the former East Germany found no association between WISC vocabulary subtest scores and current urinary mercury levels (Walkowiak et al 1998).

Memory

Low-level prenatal methylmercury exposure Verbal, visuo-spatial and visual-motor memory scores at age 7 years in the Faroe Islands birth cohort study were inversely associated with cord blood and marginally with prenatal maternal hair mercury levels (Weihe et al 1996, Grandjean et al 1997, 1999b, 2001b). The association between memory score and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). When limited to Faroese children for whom mercury levels in two prenatal maternal hair segments were available and consistent, long-term verbal memory scores at age 7 years were still inversely associated with cord blood mercury levels (Grandjean et al 2003). Data from the Faroe Islands birth cohort study on verbal memory scores at age 7 years yielded a BMDL of 4.8 µg/g for prenatal maternal hair mercury (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). The Seychelles Islands cohort study found an inverse association between verbal memory subtest scores and prenatal maternal hair mercury levels; Boston Naming test scores were *positively* associated with prenatal maternal hair mercury in boys but not girls (Davidson et al 2000). Verbal memory test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). A literature review by the United Nations Environment Programme (2002) concluded that there is some evidence that low-level prenatal methylmercury exposure can cause verbal memory deficits. A literature review concluded that prenatally exposed experimental animals had visual recognition memory deficits and abnormal auditory startle habituation (Watanabe and Satoh 1996).

Low-level postnatal methylmercury exposure Long-term verbal memory scores at age 7 years in the Faroe Islands study were not associated with current child hair or blood mercury levels (Grandjean et al 1999b). In the Seychelles Islands birth cohort study, there was a *positive* association between

nonverbal memory performance and current child hair mercury levels (Palumbo et al 2000). A small cross-sectional study of children age 6-7 years in Madeira found no association between memory test scores and maternal or child hair mercury levels (Murata et al 1999b). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found an inverse association between nonverbal memory scores and child hair mercury levels (Grandjean et al 1999a). A cross-sectional study of Amerindian children age 0-6 years in French Guiana found no association between scores on the Stanford-Binet memory test and maternal hair mercury levels (Cordier et al 2002).

Attention

Low-level prenatal methylmercury exposure In the Faroe Islands birth cohort study, sustained attention scores (Continuous Performance Test reaction times, WISC digit spans scores) at age 7 years were unfavourably associated with prenatal maternal hair and/or cord blood mercury levels (Dahl et al 1996, Grandjean et al 1997, 1999b, 2001b). The association between CPT reaction time and cord blood mercury persisted after adjustment for umbilical cord tissue PCB levels (the latter were available for about half of the cohort) (Grandjean et al 1997). The associations between attention scores and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, also found unfavourable associations between CPT reaction times and WISC digit span scores at age 7 years and cord blood mercury levels (Grandjean et al 2001a). Data from the Faroe Islands birth cohort study on sustained attention scores at age 7 years yielded a BMDL of 2.2 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found a persistent association between CPT reaction times and cord blood mercury levels (Grandjean et al 2003).

The Seychelles Islands birth cohort study found no association between attention scores at ages 7 or 9 years and prenatal maternal hair mercury levels (Myers et al 2000b, 2003). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found a statistically non-significant association between CPT reaction times and cord blood mercury levels (Weihe et al 2002). An expert panel review noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with attention deficits in two of three large epidemiologic studies (National Academy of Sciences 2000). A literature review by the United Nations Environment Programme (2002) concluded that there is some evidence that low-level prenatal methylmercury exposure can cause attention deficits.

Low-level postnatal methylmercury exposure CPT reaction times and WISC digit span scores at age 7 years were not associated with current child hair or blood mercury levels (Grandjean et al 1999b). A small cross-sectional study of children age 6-7 years in Madeira found no association between attention scores and maternal or child hair mercury levels (Murata et al 1999b). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found an inverse association between WISC digit span attention scores and current child hair mercury levels (Grandjean et al 1999a). The Seychelles Islands birth cohort study found no association between inattention and current child hair mercury levels (Myers et al 2000b).

Motor function

Low-level prenatal methylmercury exposure The Faroe Islands birth cohort study found that fine motor function scores (finger tapping speed and hand-eye coordination errors) at age 7 years were unfavourably associated with prenatal maternal hair and/or cord blood mercury levels (Dahl et al 1996, Grandjean et al 1997, 1999b, 2001b). Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, found inverse associations between finger tapping speed but not hand-eye coordination errors at age 7 years and cord blood mercury

levels (Grandjean et al 2001a). Finger tapping speed at age 7 years was not associated with current child hair or blood mercury levels (Grandjean et al 1999b). The association between finger tapping speed and cord blood mercury levels persisted among the subgroup of children whose maternal prenatal hair cord mercury levels were less than 10 µg/g (Grandjean et al 1997). Data from the Faroe Islands birth cohort study on finger tapping speeds at age 7 years yielded a BMDL of 4.3 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found persistent unfavourable associations between finger tapping speed and hand-eye coordination errors and cord blood mercury levels (Grandjean et al 2003).

In a cohort study based on follow-up of children enrolled in the Seychelles Islands cross-sectional pilot study, motor function (grooved pegboard) scores at age 9 years were *positively* associated with prenatal maternal hair mercury levels (Davidson et al 2000). Motor efficiency and finger tapping speed test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). A small cross-sectional study of children age 6-7 years in Madeira found a borderline association between failed reciprocal motor coordination and prenatal maternal hair mercury; finger tapping speed not associated with maternal or child hair mercury (Murata et al 1999b). A larger cross-sectional study of children age 7-12 years in the Amazon Basin found inverse associations between finger tapping speed and motor coordination and dexterity scores and current child hair mercury levels (Grandjean et al 1999a). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found an association between hand-eye coordination test errors and prenatal maternal hair mercury levels (Weihe et al 2002). An expert panel review noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with fine-motor function deficits in two of three large epidemiologic studies; the panel noted evidence from experimental animal studies for motor deficits from low-dose prenatal methylmercury exposure (National Academy of Sciences 2000).

Low-level postnatal methylmercury exposure After adjustment for cord blood mercury, finger tapping scores at age 7 years in the Faroe Islands birth cohort study were not associated with postnatal mercury exposure as indicated by hair mercury levels at age 12 months or 7 years (Grandjean et al 1997, 1999b). A cross-sectional study of Amerindian children age 0-6 years in French Guiana found no association between finger tapping speed or leg coordination scores and maternal hair mercury levels (Cordier et al 2002).

Visual-motor integration

Low-level prenatal methylmercury exposure In the Seychelles Islands birth cohort study, visual-motor integration scores among children followed to ages 5 and 9 years were *positively* (i.e., favourably) associated with prenatal maternal hair mercury levels (Davidson et al 1998, 2000). Using continuous values of visual-motor function scores at age 5 years in the Seychelles Islands birth cohort study, the estimated benchmark dose lower limit (BMDL) for prenatal maternal hair was 27 µg/g (Crump et al 2000). Visual-motor integration test scores among Seychellois children age 9 years were not associated with prenatal maternal hair mercury levels (Myers et al 2003). In the Faroe Islands birth cohort study, visuospatial function scores at age 7 years were not associated with prenatal maternal hair or cord blood mercury levels (Grandjean et al 1999b, 2001b). Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye glasses and with adjustment for visual contrast sensitivity, also found no association between Bender Gestalt copying errors at age 7 years and cord blood mercury levels (Grandjean et al 2001a). Data from the Faroe Islands birth cohort study on Bender Gestalt visuospatial scores at age 7 years yielded a BMDL of 6.8 µg/g for prenatal maternal hair (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al 2000). A reanalysis of the Faroe Islands birth cohort study, limited to children for whom mercury levels in two prenatal maternal hair segments were available and consistent, found an association between Bender Gestalt copying errors at age 7 years and cord blood mercury levels (Grandjean et al 2003). A literature review concluded that prenatal or postnatal methylmercury exposure affects high-order visual (contrast sensitivity, pattern recognition) systems at the cortical

level (Newland 2002). An expert panel review noted that low-level prenatal methylmercury exposure from maternal fish consumption was associated with visual-spatial deficits in two of three large epidemiologic studies (National Academy of Sciences 2000).

Postnatal methylmercury exposure In the Faroe Islands birth cohort study, visuospatial function scores at age 7 years were not associated with current child hair or blood mercury levels (Grandjean et al 1999b, 2001b). A cross-sectional study of children age 7-12 years in the Amazon Basin found an inverse association between visuospatial function scores and child hair mercury levels (Grandjean et al 1999a). A cross-sectional study of Amerindian children age 0-6 years in French Guiana found no association between scores on the Stanford-Binet copying test of visuospatial organization and maternal hair mercury levels (Cordier et al 2002). A literature review concluded that prenatal or postnatal methylmercury exposure affects high-order visual (contrast sensitivity, pattern recognition) functions at the cortical level with effects being strongly age-dependent (Newland 2002).

Visual-evoked potential latencies

Low-level prenatal methylmercury exposure There was no association between visual-evoked potential latencies at age 7 years and cord blood mercury in the Faroe Islands birth cohort study (Grandjean et al 1997). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found no association between brainstem visual-evoked potential latencies and prenatal maternal hair mercury levels (Weihe et al 2002).

Low-level prenatal methylmercury exposure A cross-sectional study in Germany found that no association between visual-evoked brainstem potential latencies at age 7 years and current urinary mercury levels (Altmann et al 1998). In a cross-sectional study of children age 6-7 years in Madeira, 1 of 4 measured pattern-reversal visual evoked potential latencies was associated with current maternal but not child hair mercury levels (Murata et al 1999b).

Other visual function tests

A cross-sectional study in Germany found that contrast sensitivity (an indicator of visual cortical function) at age 5-7 years was inversely associated with current urinary mercury levels (Altmann et al 1998).

Auditor-evoked potential latencies and interpeak intervals

Low-level prenatal methylmercury exposure Brain stem auditory-evoked potential latencies and interpeak intervals among children at ages 7 and 14 years were associated with prenatal maternal hair and cord blood mercury levels in the Faroe Islands birth cohort study (Grandjean et al 1997, Murata et al 1999b, 2004). Analysis of combined from children in the Faroe Islands and Madeira studies yielded a benchmark dose for prenatal maternal hair mercury of 9.5 µg/g for a doubling of a 5% prevalence of abnormal auditory-evoked potential latencies at 40 Hz, with similar results at 20 Hz (Murata et al 2002). A small retrospective cohort study of Inuit children age 7-12 years in Greenland found associations between brainstem auditory-evoked potential latencies and prenatal maternal hair mercury levels (Weihe et al 2002).

Low-level postnatal methylmercury exposure Brain stem auditory-evoked potential latencies and interpeak intervals among children at ages 7 and 14 years were not associated with current child hair mercury levels in the Faroe Islands birth cohort study (Grandjean et al 1997, Murata et al 1999b, 2004). Brain stem auditory-evoked potential latencies were associated with current maternal but not current child hair mercury levels in a cross-sectional study of children age 6-7 years in Madeira (Murata et al 1999a). Reports from a small cross-sectional study of Ecuadoran children age 3-15 years indicated associations between certain brainstem auditory-evoked potential latencies and intervals and current blood mercury levels (Counter et al 1998, 2003).

Other auditory function indices

Low-level methylmercury exposure In the Seychelles Islands pilot study, reevaluation of a subgroup of children at age 5 years showed that the auditory comprehension scores were inversely associated with prenatal maternal hair mercury levels (Myers et al 1995a). A small cross-sectional study of Ecuadoran children age 3-15 years found an inverse (i.e., favourable) association between hearing threshold at 3 kHz in the right ear, but not in left ear, and current blood mercury levels (Counter et al 1998). A literature review concluded that prenatal or postnatal methylmercury exposure affects auditory systems at the cortical level (Newland 2002).

Academic performance

Low-level prenatal methylmercury exposure A reanalysis of a New Zealand birth cohort study found that reading concept, grammar completion and understanding scores at ages 6-7 years were inversely associated with prenatal maternal hair mercury levels (Crump et al 1998). In the Seychelles Islands birth cohort study, there were no associations between applied problem test scores at age 9 years and prenatal maternal child hair mercury levels (Myers et al 2000b, 2003).

Low-level postnatal methylmercury exposure A birth cohort study in Michigan found an association between poor spelling scores at age 11 years and current hair mercury levels (Jacobson and Jacobson 1996). In the Seychelles Islands birth cohort study, applied problem scores at ages 5 years were *positively* associated with current hair mercury levels (Davidson et al 1998).

Problem behaviours

Low-level prenatal methylmercury exposure The Seychelles Islands birth cohort study found no associations between aggressive and other problem behaviours and prenatal maternal hair mercury levels (Myers et al 2000b). Hyperactivity among Seychellois children age 9 years was inversely, i.e., favourably, associated with prenatal maternal hair mercury levels (Myers et al 2003).

Low-level postnatal methylmercury exposure The Seychelles Islands birth cohort study found no associations between aggressive and other problem behaviours and current child hair mercury levels (Myers et al 2000b).

General

Methylmercury An EPA report to Congress concluded that neurotoxicity is the most sensitive indicator of toxicity from elemental and organic mercury, the main effects in humans and multiple animal species being motor and sensory, especially sensorimotor integration (U.S. Environmental Protection Agency 1997). The latter report also concluded that the reference dose (RfD) for methylmercury, based on Iraqi data for developmental milestone delay in prenatally exposed children, was 0.1 µg/kg/day. After adjustment for cord blood mercury levels in the Faroe Islands birth cohort study, none of the neuropsychologic test scores at age 7 years was associated with current child hair mercury levels, i.e., the associations were with prenatal but not postnatal methylmercury exposure (Grandjean et al 1997). A literature review concluded that high-level prenatal methylmercury exposure disrupts neuronal proliferation and migration, causing widespread damage in the developing brain and the clinical appearance of cerebral palsy; only the most severely poisoned cases having peripheral nerve damage (Clarkson 1997). Another review stated that prenatal maternal consumption of marine fish from non-industrially polluted regions does not cause adverse neurodevelopmental outcomes (Myers and Davidson 1998). A summary of the 1997 EPA report to Congress noted that there is a steep dose-response relationship between methylmercury and neurotoxicity in experimental animals; subclinical toxicity occurs at 1.1 µg/g in diet, ataxia at 1.8 µg/g and

death at 4.8 µg/g (Mahaffey 1999). An expert panel concluded that animal studies show cognitive, motor and sensory deficits from low-dose prenatal methylmercury exposure (National Academy of Sciences 2000).

Elemental mercury A literature review concluded that the main sources of childhood exposure to elemental mercury have been accidental spills indoors and dental amalgam (a mixture of elemental mercury and other elements) and that there are no proven health effects of dental amalgam (Clarkson 1997).

6. Immune function

Reference, location	Design	Exposure	Results	Association	DR	Covariates
(Herrstrom et al. 1994), Sweden	Cross-sectional study; 41 children age 15 yr; assessed immune function	Measured number of amalgam fillings (median n=4), plasma mercury levels (median 0.33 and 0.42 µg/L in boys and girls)	Among several immune function indicators (cell counts, immunoglobulin levels), only plasma IgA levels associated with plasma mercury among children age 15 yr; mean IgA levels, children with plasma mercury >median vs <median	1.8 vs 1.1 g/L, p=0.009		Sex
			History of allergic diseases among children age 15 yr not associated with plasma mercury level; mean plasma mercury, allergic vs non-allergic children	1.5 vs 1.8 nM/L, p=0.21		
(Herrstrom et al. 1997)	Cross-sectional study, 77 students, average age 19 yr, half with asthma or other allergic diseases; assessed plasma immunoglobulin levels	Number of dental amalgam fillings; plasma mercury (median 0.26 and 0.30 µg/L in males and females)	Among plasma immunoglobulin fractions, only IgG ₂ was associated with plasma mercury levels; Spearman rank correlation coefficient	r _s =0.33, p=0.003	+	
(Powell et al. 1999), USA	Review of autoimmune disease and environmental agents		Animals – mercuric chloride induces antibodies against renal glomerular basement membrane and immune-complex deposition in kidneys			
(Ten Tusscher et al. 2003), The Netherlands	Birth cohort, 27 children breast-fed for at least 2 mos; examined at age 8 yr	Measured breast milk dioxin-TEQ levels at baseline and estimated total lactational exposure; also measured children's urinary mercury (all values < 1 µg/L) and blood lead (range 1.6-2.4 µg/dL) levels	Blood immune function indices not associated with urinary mercury or blood lead levels (results stated without supporting data)			

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Immune function: summary

In two small Swedish cross-sectional studies of youth, plasma IgA and IgG₂ levels were associated with plasma mercury levels (Herrstrom et al 1994, 1997). A history of allergic disease was not associated with plasma mercury (Herrstrom et al 1994). A birth cohort study in the Netherlands found no associations between immune function indices and current urinary mercury levels (Ten Tusscher et al 2003). A review of toxicologic literature concluded that inorganic mercury induces antibodies against renal glomerular basement membrane and renal deposition of immune-complexes (Powell et al 1999).

7. Other health effects

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
(Warkany and Hubbard 1951), USA	Case-control study, 41 cases of infantile acrodynia, age 6 mos to 13 yr, 60 controls; acrodynia is characterized by pink hands and feet, desquamation, scarlet cheeks and tip of nose, alopecia, salivation, loss of teeth, occasional loss of nails or phalanges, excessive perspiration, hypotonia, itching, burning pain in extremities, elevated pulse and blood pressure, photophobia, insomnia, apathy alternating with irritability	Detected urinary mercury in 93% of cases and 15% of controls; median level in cases was 100 µg/L; exposure sources included mercurous chloride (calomel), teething powders or worm pills containing mercurous chloride, ammoniated mercury ointment and mercury bichloride used to rinse diapers	Acrodynia associated with elevated urinary mercury levels; odds ratio (calculated from data in paper)	72 (19-323)		
(Gotelli et al. 1985), Argentina	Cross-sectional study, 509 infants exposed to diapers treated with phenylmercury and 166 unexposed infants; measured urinary total protein and γ-glutamyl transpeptidase (γ-GT)	Measured urine and hair mercury	Urinary γ-GT associated with urinary mercury excretion rates; segmented regression analysis indicated a threshold at about 6 µg/kg body wt/day (result stated without further data)			
(Lauwerys et al. 1985), Belgium	Cohort study, 103 workers exposed to airborne elemental mercury, 85 workers exposed to airborne manganese salts, 182 men in comparison group; assessed fertility of exposed men before and after exposure; expected number of children based on fertility of comparison group	Average blood mercury level among exposed men was 1.5 µg/dL; corresponding urinary mercury level was 52 (range 5.1-272 µg/g) creatinine	No association between fertility and mercury exposure (observed vs expected number of children)	59 vs 65.8 (p>0.05)		Groups similar with regard to age, age of wives, duration of employment, smoking, alcohol, education, wife's occupation

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
(Herrstrom et al. 1995), Sweden	Cross-sectional study, 48 students age 17-22 yr; measured urinary albumin, α 1- microglobulin, kappa and lambda light chains, and N-acetyl- β -D-glucosaminidase	Number of amalgam surfaces, urinary mercury (median 2.3 μ g/g creatinine)	Urinary protein levels not associated with number of amalgam tooth surfaces or urinary mercury level; Pearson's correlation coefficients	albumin r=0.08, p=0.65 α 1- microglobulin r=-.02, p=0.45 NAG1 r=0.05, p=0.92		
(Wulff et al. 1996), Ronnskar Sweden	Birth cohort study; 120 birth defects among 2,724 births in population living near copper smelter and 582 birth defects among 15,191 births in comparison region	High environmental levels of lead, arsenic, cadmium, mercury; exposure index was residential proximity to copper smelter	Borderline increased risk of chromosomal abnormalities	2.6 (0.9-6.7)		
(Paul 1997), USA	Review of literature on developmental and reproductive outcomes and occupational exposures		Limited evidence of associations between reduced semen quality and occupational exposure to inorganic mercury			
			Limited evidence of reduced fertility among women occupationally exposed in dental offices (elemental mercury vapour, nitrous oxide)			
(U.S. Environmental Protection	Literature review (report to Congress)		Inorganic mercury is a possible human carcinogen and a possible			

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
Agency 1997)			germ cell mutagen; organic mercury is a possible human carcinogen and a probable human germ cell mutagen			
			Childhood blood pressure and heart rate variability associated with prenatal maternal hair mercury at levels below 10 µg/g			
(Clarkson 1997)	Literature review	Inorganic mercury – the main sources of childhood exposure have included teething powders used for infants during the mid 20 th century and disinfectants used in washing diapers	Acrodynia and renal toxicity in children	+		
		Elemental mercury – the main sources of childhood exposure have been accidental spills indoors and dental amalgam	High-level prolonged exposure ($\geq 100 \mu\text{g}/\text{m}^3$) of adults causes renal tubular damage			
(Spinelli et al. 1997), Italy	Retrospective cohort study, 622 women who delivered liveborn infants in 4 hospitals during early 1993; self-reported time to pregnancy	Mother-reported parental occupational exposures	Likelihood of conception inversely associated with paternal preconceptional occupational exposure to welding fumes (fecundability ratio, exposed vs unexposed)	0.8 (0.6-1.0)		Maternal age, parity, intercourse frequency, smoking, alcohol, coffee, tea
(Younglai et al.	Case report; boy age 5 yr with	Bedroom painted with latex	Neurologic signs and			

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
1998), USA	acrodynia	paint containing phenyl mercuric propionate; estimated air mercury level 210 µg/m ³ ; urinary mercury 90 µg/L	symptoms included irritability, mood changes, photophobia, anorexia, insomnia and hypotonia; other symptoms included perspiration, desquamation and pink colour of hands, hypertension and abdominal and joint pain			
(Sorensen et al. 1999), Faroe Islands	Birth cohort study, 917 children age 6-7 yr; measured blood pressure and other cardiovascular parameters	GM mercury in cord blood 23 (range 13-41 µg/L), prenatal maternal hair 4.3 (range 2.6-7.7 µg/g), child hair at 12 mos 1.1 (range 0.7-1.9 µg/g), child hair at age 7 yr 3.0 (range 1.7-6.1 µg/g) (from Grandjean et al, 1997)	Diastolic blood pressure associated with cord blood mercury; blood pressure increment for a cord blood mercury increase from 1 to 10 µg/L	13.9 mm Hg (7.4-20)	+	Weight, maternal hypertension
			Systolic blood pressure associated with cord blood mercury; blood pressure increment for a cord blood mercury increase from 1 to 10 µg/L	14.6 mm Hg (8.3-21)	+	Weight
			In boys, heart rate variability was inversely associated with cord blood mercury; change in variability for a cord blood mercury increment from 1 to 10 µg/L	-47% (-68, -14)	+	

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
(Osius et al. 1999)	Cross-sectional study of 320 children age 7-10 yr potentially exposed to PCBs, lead, cadmium, and mercury from a toxic waste incinerator;	Measured whole blood PCBs, thyroid-stimulating hormone (TSH), free thyroxine (T4), and free triiodothyronine (T3), cadmium, and lead levels and mercury levels in 24-hr urine samples	Thyroid hormone levels among children age 7-10 yr not associated with current urine mercury levels; β -coefficients for urinary mercury $>0.2 \mu\text{g/L}$	TSH $\beta=0.18$, $p=0.17$ FT ₄ $\beta=0.05$, $p=0.73$ FT ₃ $\beta=-0.09$, $p=0.47$		Child sex, age, ETS exposure, fish consumption frequency, whole blood PCBs, urinary cadmium and lead
(Schafer et al. 1999), Germany	Cross-sectional study, 2200 children aged 5-14 yr, from 2 industrial regions and 1 agricultural comparison region; screened by dermatologist for atopic eczema (51 cases identified)	Measured urinary arsenic, cadmium and mercury and blood lead and mercury	No association between atopic eczema among children age 5-14 yr and current blood or urinary mercury levels; prevalence of eczema by urinary mercury quartile (lowest to highest)	2.2, 4.3, 2.7 and 2.8%		Sex, age, location, parental history, SES, pets, environmental tobacco smoke, heating system
(National Academy of Sciences 2000)	Literature review		There is some evidence in animals and humans that low-level methylmercury has adverse effects on the developing and adult cardiovascular system including blood pressure regulation, heart rate variability and heart disease			
			There is inadequate evidence for carcinogenicity of			

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
			methylmercury			
(United Nations Environment Programme, 2002)	Literature review		Some evidence that low-level prenatal methylmercury exposure can cause cardiovascular effects in children (heart rate variability, increased blood pressure)			
(Watson et al. 2003), USA	Monitoring system (Toxic Exposure Surveillance System (TESS)), data from 64 participating US poison centers, 2002		9,723 reports of children age 0-19 yr who were exposed during 2002 to elemental mercury from various sources including thermometers; among all elemental mercury exposure reports (persons of all ages), about 2% had moderate or severe health outcomes			
(Burbure et al. 2003), France	Cross-sectional study, 400 children age 8-12 yr, living near two nonferrous smelters and age/sex-matched comparison group from unpolluted neighbouring regions; assessed renal function by measuring urinary proteins (total, albumin, transferrin, β 2-microglobulin, retinol-binding protein, brush border antigen, NAG)	Measured blood cadmium (mean 0.5 μ g/L in all 4 sex/region subgroups) and urinary mercury, blood lead (mean 2.7-4.2 μ g/dL in 4 sex/region subgroups) and urinary mercury (0.9-1.2 μ g/g creatinine)	Urinary protein levels among children age 8-12 yr associated with urinary cadmium but not mercury levels; result stated without supporting data			Age, sex, body mass index, region
(Holmes et al.	Hospital-based case-control	Mother-reported information	Hair mercury levels in the	0.5 vs 3.6		Matched for age

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
2003)	study, 94 cases autism from USA, Canada, UK and Mexico, 45 controls from USA, age 2-15 yr; mother-reported information on severity of autism	on diet, dental amalgam fillings; measured mercury levels in hair samples saved from first hair cut during infancy	autistic group were lower than among controls; mean levels, cases vs controls	ppm, p<0.01		and sex
			Hair mercury levels inversely associated with mother-reported autism severity; mean levels for mild, moderate and severe symptoms	0.8, 0.5, 0.2 ppm		
(Ip et al. 2004)	Case-control study, 82 cases autism, 55 controls, avg age 7-8 yr	Measured blood and hair mercury levels	Autism not associated with hair or blood mercury levels; mean levels, cases vs controls	blood 20 vs 18 nM/L, p=0.15 hair 2.3 vs 2.1 ppm, p=0.8		
(Grandjean et al. 2004), Faroe Islands	Longitudinal cohort study, 878 children recruited during 1986-1987 and followed to age 14 yr; assessed blood pressure, heart rate variability	Measured mercury in cord blood, prenatal maternal hair, child's hair at ages 7 and 14 yr	Systolic and diastolic blood pressure and heart rate at age 14 yr not associated with mercury exposure indices; estimated effect of a doubling of methylmercury exposure; results for systolic blood pressure shown	cord blood 0.045 mm Hg, p=0.84 hair age 7 0.040 mm Hg, p=0.83 hair age 14 -0.017 mm Hg, p=0.91		Birth weight, maternal hypertension risk, prenatal smoking, child age, sex, height, weight
			Heart rate variability at age 14 yr inversely associated with cord blood	cord blood -6.7, p=0.04	+	As above

Reference, location	Design	Exposure	Results	Association	DR ^a	Covariates
			mercury levels; estimated % change from a doubling of methylmercury exposure; results for low frequency power shown	hair age 7 -3.0, p=0.27 hair age 14 -2.1, p=0.40		

Other health effects summary

Acrodyndia

This pediatric condition is characterized by pink hands and feet, desquamation, scarlet cheeks and other signs/symptoms; sporadic cases have been caused by exposure to mercurous chloride (calomel), teething powders or worm pills containing mercurous chloride, ammoniated mercury ointment and mercury bichloride used to rinse diapers (see Warkany and Hubbard 1951 below). A case of acrodyndia in a boy age 5 years was linked to substantially elevated indoor air elemental mercury levels ($210 \mu\text{g}/\text{m}^3$) in a house painted with latex paint containing phenyl mercuric propionate; the child's urinary mercury level was $90 \mu\text{g}/\text{L}$ (Younglai et al 1998). A literature review concluded that inorganic mercury can cause acrodyndia in children (Clarkson 1997).

Male fertility

A small cohort study found no association between a crude index of male fertility (number of children) and occupational exposure to airborne elemental mercury (Lauwerys et al 1985). A retrospective cohort study in Italy found an inverse association between likelihood of conception and preconceptual paternal occupational mercury exposure (Spinelli et al 1997).

Female fertility

A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced female fertility and occupation in dental offices (likely exposures to elemental mercury and nitrous oxide) (Paul 1997).

Semen quality

A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced semen quality and occupational exposure to inorganic mercury (Paul 1997).

Kidney function abnormalities

A cross-sectional study of infants exposed to diapers treated with a phenyl mercuric fungicide in Argentina found an association between urinary γ -glutamyl transpeptidase and urinary mercury excretion rates with an apparent threshold of about $6 \mu\text{g}/\text{kg}$ body wt/day (Gotelli et al 1985). A small cross-sectional study of students age 17-22 years found no association between urinary protein levels and number of amalgam tooth surfaces or urinary mercury levels (Herrstrom et al 1995). A larger cross-sectional study of children age 8-12 years in France found no association between urinary proteins and urinary mercury levels (Barbure et al 2003). A literature review noted that childhood inorganic mercury exposure caused renal toxicity in children (Clarkson 1997).

Cardiovascular abnormalities: blood pressure

The Faroe Islands birth cohort study found that diastolic and systolic blood pressure among children age 6-7 years were associated with cord blood mercury levels (Sorensen et al 1999). The EPA report to Congress and two other expert panel reviews found limited epidemiologic evidence that childhood blood pressure was associated with low-level prenatal methylmercury exposure (U.S. Environmental Protection Agency 1997, National Academy of Sciences 2000, United Nations Environment Programme 2002). Follow-up of Faroese children to age 14 years showed no associations between diastolic or systolic blood pressure and cord blood or childhood hair mercury levels (Grandjean et al 2004).

Cardiovascular abnormalities: heart rate variability

The Faroe Islands birth cohort study found that heart rate variability in boys was inversely associated with cord blood mercury (Sorensen et al 1999). The EPA report to Congress and two other expert panel reviews found limited epidemiologic evidence that heart rate variability was associated with low-level prenatal methylmercury exposure (U.S. Environmental Protection Agency 1997, National Academy of Sciences 2000, United Nations Environment Programme 2002). Follow-up of Faroese children to age 14 years showed that heart rate variability was inversely associated with cord blood but not childhood hair mercury levels (Grandjean et al 2004).

Thyroid function abnormalities

A cross-sectional study of children age 7-10 years in Germany found no association between thyroid hormone levels (TSH, T3, T4) and urine mercury levels (Osius et al 1999).

Genotoxicity

A birth cohort study in Sweden found an increased risk of chromosomal abnormalities among infants of women who lived near a smelter that emitted mercury and other toxicants (Wulff et al 1996). The EPA report to Congress on mercury concluded that inorganic mercury is a possible germ cell mutagen and that organic mercury is a probable human germ cell mutagen (U.S. Environmental Protection Agency 1997).

Cancer

The EPA report to Congress on mercury concluded that inorganic and organic mercury are possible human carcinogens (U.S. Environmental Protection Agency 1997). Other expert panels concluded that there is inadequate evidence for carcinogenicity of methylmercury (National Academy of Sciences 2000, United Nations Environment Programme 2002). No epidemiologic studies have assessed the potential role of prenatal or childhood mercury exposure in childhood or adult cancers.

Atopic eczema

A cross-sectional study of children age 5-14 years found no associations between atopic eczema and urinary or blood mercury levels (Schafer et al 1999).

Elemental mercury poisoning

The health effects of mercury vapor have been known since ancient times with high exposure causing three major signs, i.e., skin rash, tremor and gingivitis (Clarkson 1997). There continue to be sporadic reports of clinically apparent childhood mercury poisoning caused by indoor exposure to elemental mercury vapour (Centers for Disease Control and Prevention 1995). In the USA during 2002, there were 9723 reports of children age 0-19 years who were exposed to elemental mercury from various sources including thermometers; among all elemental mercury exposure reports (persons of all ages), about 2% had moderate or

severe health outcomes (Watson et al 2003). The latter data came from the Toxic Exposure Surveillance System (TESS) based on data from 64 participating US poison centers.

Autism

A small hospital-based case-control study in North America and the UK found an *inverse* association between autism among children age 2-15 years and current hair mercury levels (Holmes et al 2003). Another case-control study found no association between autism and current blood or hair mercury levels (Ip et al 2004).

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