Available online at www.sciencedirect.com

SCIENCE DIRECT®

Toxicology and Applied Pharmacology 198 (2004) 209–230

Toxicology and Applied Pharmacology

www.elsevier.com/locate/ytaap

Review

Mercury exposure in children: a review

S. Allen Counter[a,*] and Leo H. Buchanan[b]

[a] *Department of Neurology, Massachusetts General Hospital, Harvard Biological Laboratories, Harvard Medical School, Cambridge, MA 02138, USA*
[b] *Harvard University Health Services, Shriver Center/University of Massachusetts Medical School, Waltham, MA 02452, USA*

Received 4 July 2003; accepted 13 November 2003
Available online 9 April 2004

Abstract

Exposure to toxic mercury (Hg) is a growing health hazard throughout the world today. Recent studies show that mercury exposure may occur in the environment, and increasingly in occupational and domestic settings. Children are particularly vulnerable to Hg intoxication, which may lead to impairment of the developing central nervous system, as well as pulmonary and nephrotic damage. Several sources of toxic Hg exposure in children have been reported in biomedical literature: (1) methylmercury, the most widespread source of Hg exposure, is most commonly the result of consumption of contaminated foods, primarily fish; (2) ethylmercury, which has been the subject of recent scientific inquiry in relation to the controversial pediatric vaccine preservative thimerosal; (3) elemental Hg vapor exposure through accidents and occupational and ritualistic practices; (4) inorganic Hg through the use of topical Hg-based skin creams and in infant teething powders; (5) metallic Hg in dental amalgams, which release Hg vapors, and Hg^{2+} in tissues. This review examines recent epidemiological studies of methylmercury exposure in children. Reports of elemental Hg vapor exposure in children through accidents and occupational practices, and the more recent observations of the increasing use of elemental Hg for magico-religious purposes in urban communities are also discussed. Studies of inorganic Hg exposure from the widespread use of topical beauty creams and teething powders, and fetal/neonatal Hg exposure from maternal dental amalgam fillings are reviewed. Considerable attention was given in this review to pediatric methylmercury exposure and neurodevelopment because it is the most thoroughly investigated Hg species. Each source of Hg exposure is reviewed in relation to specific pediatric health effects, particularly subtle neurodevelopmental disorders.

Keywords: Hg vapors; Mercury; Fetal exposure

Introduction

Over the past century, there has been an increasing awareness throughout the world of the health and developmental risks associated with environmental exposure to toxic metals, such as, lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (AS). While exposure to toxic levels of any of these environmental contaminants may result in impaired health in adults, the toxicological effects of these metal are often more devastating in the developing central nervous system and general physiological systems of children. Although Pb is perhaps the most publicized and well known of the pediatric metal intoxicants, Hg is at least equally toxic if less well known.

Mercury is ubiquitous in the global environment and derives from both natural sources and human enterprise. The presence of Hg in fish, thermometers, dental amalgams, vaccine preservatives, and in the atmosphere has made this particular toxic metal an increasing focus of health authorities and interest groups. Many industrialized nations have established procedures and policies to assess, minimize, and prevent exposure to Hg. However, many developing, low-income countries have only recently begun to identify sources of toxic Hg exposure in the milieu and diet, and to establish ways of protecting children, adults, and nonhuman species.

The recent popular media attention given to pediatric Hg exposure reflects the growing concerns by the general public, health officials, and policymakers about the detrimental effects of Hg on the health and development of exposed children. In the United States, for example, several federal agencies have examined data on Hg exposure and its consequences, and have attempted to establish standards for

* Corresponding author. The Biological Laboratories, Neurology/ Harvard Medical School, 16 Divinity Avenue, Cambridge, MA 02138. Fax: +1-617-496-1443.
E-mail address: allen_Counter@harvard.edu (S.A. Counter).

0041-008X/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.taap.2003.11.032

Table 1
Summary comparing toxicologically relevant mercury species (from Table 2-2 of the National Research Council, Committee on the Toxicological Effects of Methylmercury, 2000. Toxicological Effects of Methylmercury, National Academy Press,Washington D.C., with permission)

Methylmercury (CH_3Hg^+)	Elemental mercury (Hg^0)	Mercuric mercury (Hg^{2+})
Sources of exposure		
Fish, marine mammals, crustaceans, animals and poultry fed fish meal	dental amalgams, occupational exposure, Caribbean religious ceremonies, fossil fuels, incinerators	oxidation of elemental mercury or demethylation of MeHg; deliberate or accidental poisoning with $HgCl_2$
Biological monitoring		
Hair, blood, cord blood	urine, blood	urine, blood
Toxicokinetics		
Absorption		
Inhalation: vapors of MeHg absorbed	*Inhalation*: approximately 80% if inhaled dose of Hg^0 readily absorbed	*Inhalation*: aerosols of $HgCl_2$ absorbed
Oral: approximately 95% of MeHg in fish readily absorbed from GI tract	*Oral*: GI absorption of metallic Hg is poor; any released vapor in GI tract converted to mercuric sulfide and excreted	*Oral*: 7–15% of ingested dose of $HgCl_2$ absorbed from the GI tract; absorption proportional to water solubility of mercuric salt; uptake by neonates greater than adults
Dermal: in guinea pigs, 3–5% of applied dose absorbed in 5 h	*Dermal*: average rate of absorption of Hg^0 through human skin, 0.024 ng/cm^2 for every 1 mg/m^3 in air	*Dermal*: in guinea pigs, 2–3% of applied dose of $HgCl^2$ absorbed
Distribution		
Distributed throughout body since lipophilic; approximately 1–10% of absorbed oral dose of MeHg distributed to blood; 90% of blood MeHg in RBCs MeHg–cysteine complex[a] involved in transport of MeHg into cells	rapidly distributed throughout the body since it is lipophilic	highest accumulation in kidney; fraction of dose retained in kidney dose dependent
Half-life in blood, 50 days; 50% of dose found in liver; 10% in head	half-life in blood, 45 days (slow phase); half-life appears to increase with increasing dose	half-life in blood, 19.7–65.6 days; first phase, 24 days, second phase, 15–30 days
Readily crosses blood–brain and placental barriers	readily crosses blood–brain and placental barriers	does not readily penetrate blood–brain or placental barriers in neonate, mercuric Hg not concentrated in kidneys; therefore, more widely distributed to other tissues in fetus and neonate, blood–brain barrier incompletely formed, so mercuric Hg brain concentrations higher than those in adults
Biotransformation		
MeHg slowly demethylated to mercuric Hg (Hg^{2+})	Hg^0 in tissue and blood oxidized to Hg^{2+} by catalase and hydrogen peroxide (H_2O_2); H_2O_2 production the rate-limiting step	Hg^0 vapor exhaled by rodents following oral administration of mercuric Hg
Tissue macrophages, intenstinal flora, and fetal liver are sites of tissue demethylation		mercuric Hg not methylated in body tissues but GI microorganisms can form MeHg
Mechanisms of demethylation unknown; free radicals demethylate MeHg in vitro; bacterial demethylation enzymes studied extensively; none has been characterized or identified in mammalian cells		
Does not bind or induce metallothionein		binds and induces metallothionein
Excretion		
Daily excretion, 1% of body burden; major excretory route is bile and feces; 90% excreted in feces as Hg^{2+}; 10% excreted in urine as Hg^{2+} Lactation increases clearance from blood; 16% of Hg in breast milk is MeHg	excreted as Hg^o in exhaled air, sweat, and saliva, and as mercuric Hg in feces and urine	excreted in urine and feces; also excreted in saliva, bile, sweat, exhaled air, and breast milk
Half-life elimination		
(Whole body) 70–80 days; dependent on species, dose, sex, and animal strain	58 days	1–2 months

Table 1 (*continued*)

Methylmercury (CH_3Hg^+)	Elemental mercury (Hg^0)	Mercuric mercury (Hg^{2+})
Toxicodynamics		
Critical target organ		
Brain, adult and fetal	brain and kidney	kidney
Causes of toxicity		
Demethylation of MeHg to Hg^{2+} and intrinsic toxicity of MeHg	oxidation of Hg^0 to Hg^{2+}	Hg^{2+} binding to thiols in critical enzyme (e.g., cysteine) and structural proteins
Mobilization		
DMPS, DMSA	after oxidation to Hg^{2+}: DMPS, DMSA	DMPS, DMSA
Possible antagonists		
Selenium, garlic, zinc		
Latency period		
In Iraq, from weeks to month; in Japan, more than a year; differences suggested to be caused by Se in fish; no toxic signs during latency period		

$HgCl_2$, mercuric chloride; DMPS, 2,3-dimercapto-1-propane sulfonate; DMSA, meso-2,3-dimercaptosuccinic acid; GI, gastrointestinal tract; RBC, red blood cells.

[a] MeHg–cysteine complex is structurally analogous to methionine.

health-based biological limits for Hg exposure in children and pregnant women, and have informed the public of the associated health hazards through advisories (ATSDR, 1999; EPA, 1997).

The element Hg is classified as a heavy metal (at. wt.: 200.59) and exists in three species: elemental mercury (Hg^0) (also known as metallic mercury), inorganic mercury compounds (I-Hg) (primarily mercuric chloride), and organic mercury [primarily methylmercury (MeHg)]. Exposure to each species results in both specific and general toxicological effects in children and adults. The toxicological features of each species are summarized in Table 1.

There are several earlier and more contemporary reviews of the toxicology of Hg available to the reader that cover a spectrum of findings ranging from sources of Hg exposure to the toxicity of different species and biological outcomes (ATSDR, 1992, 1999; Chang, 1977; Clarkson, 2002; Koos and Longo, 1976; NRC, 2000; Satoh, 2000; Sweet and Zelikoff, 2001). The American Academy of Pediatrics, for example, issued a recent technical report reviewing the general health effects of Hg exposure (Goldman and Shannon, 2001). One of the more comprehensive, critical reviews of the general effects of Hg exposure was compiled by Ratcliffe et al. (1996).

In this review, we cite and report the findings of a wide spectrum of studies on Hg exposure in children. Additionally, this review examines some of the studies of Hg exposure in adults and in experimental animals that may have implications for the effects of Hg exposure on children. Specifically, this review examines studies of Hg exposure in children, including fetal exposure (as a result of maternal consumption of fish, inhalation of Hg vapors, and the use of Hg-containing topical creams), neonatal and infant exposure from the same sources, as well as from breast milk of lactating mothers, fish consumption in young children, and finally dental amalgam in older children. Studies of the pediatric health effects of different forms of Hg exposure, including MeHg, ethylmercury, Hg^0 vapors, and I-Hg are covered. Since the most thoroughly investigated Hg species is, MeHg, particularly in the recent large cohort studies (Davidson et al., 1998, 2000; Grandjean et al., 1997, 1998; Myers et al., 2003), this review gives substantial attention to pediatric MeHg intoxication and neurodevelopment. Secondly, this review examines exposure to ethylmercury from pediatric vaccines that contain the controversial preservative thimerosal. The increasing number of clinical reports of Hg^0 vapor exposure in children through accidents and occupational and ritualistic practices is reviewed. Recent observations of the widespread use of Hg^0 in modern, urban communities for magico-religious purposes, and its impact on children are covered. The significance of maternal dental amalgam fillings on fetal Hg levels and the Hg exposure levels of children with dental amalgams are also discussed. Finally, we review the use of I-Hg in infant teething powders and in popular Hg-based beauty creams, which may be used by mothers, an in some cases applied by parents to children to lighten their skins, or may affect the fetus through placental transfer. Reports of Hg intoxication among some indigenous peoples who are frequently exposed to Hg^0 vapors in occupations, such as gold mining, and MeHg through dietary exposure from industrial discharge into traditional fishing waterways, are covered in a subsection.

Biological effects of mercury exposure: an overview

Any discussion of the effects of Hg exposure on humans must proceed from a basic understanding of the effects of Hg on targeted cells in biological systems. Since studies of these effects cannot be ethically conducted in humans, experimental animal investigations serve to inform the subject of the specific biological effects of Hg exposure

that may lead to neurological damage and other health impairments in humans (Table 1). In an attempt to elucidate the underlying mechanisms of Hg intoxication in children, it is instructive to review some experimental animal studies on Hg exposure. The cytotoxicity of each species of Hg has been the subject of considerable scientific interest.

Methylmercury

Some experimental studies have shown that MeHg accumulates in the rat brain in approximately 5 min following intravenous injection (Hirayama, 1985; Thomas and Smith, 1982), and in the mouse brain about 4 h after ingestion (Sager et al., 1982). At the cellular level, Shafer et al. (2002) observed that prolonged exposure to MeHg in low concentrations reduced both Na^+ and Ca^{2+} ion currents in the membrane channels of cultured cells. At the transmembrane receptor level, Parran et al. (2003) found that MeHg inhibited trkA (tyrosine kinase receptor) autophosphorylation and reduced neurite outgrowth in PC 12 cells by disrupting nerve growth factor stimulated trkA receptor activity.

Elemental mercury

Numerous experimental animal studies have been conducted to elucidate the effects of Hg^0 exposure, and the cellular and physiological mechanisms involved with Hg^0 toxicity. For example, heavy Hg deposits were found in the alveolar macrophages of the lungs of Hg^0-vapor-exposed rats by Moller-Madsen (1992). Further, animals exposed to Hg^0 vapor at a level of 500 μg Hg/m^3 in air showed CNS Hg staining in the cerebral cortex, thalamus, corpus striatum, mesencephalic nucleus of the trigeminal nerve, cerebellar nuclei, and motor neurons of the spinal cord (Moller-Madsen, 1992). Yoshida et al. (1999a) found lung damage in mice that had been exposed to Hg^0 vapors. They also reported that the lungs of metallothionein-null mice exposed to Hg^0 vapors were significantly more impaired than that of matched wild types, suggesting a protective role for metallothionein against pulmonary toxicity of Hg^0 vapor (Yoshida et al., 1999b). Sorensen et al. (2000) reported that Hg^0 vapor intoxication induced significant neuronal reduction in the CNS, particularly in the cerebellum of rats. They further suggested that Hg^0 may have a different toxicological profile from that of MeHg, which may affect both the CNS and the peripheral nervous system. Evidence of Hg^0 poisoning of the fetus from inhaled Hg^0 vapors has been found in the developing blood vessels, sensory ganglia, and nervous system of mice exposed in the late prenatal and early neonatal stages to Hg^0 vapors at levels of 500 μM^3 (Pamphlett and Kum-Jew, 2001).

In an investigation of the long-term effects of prenatal Hg vapor exposure on learning and motor function, Newland et al. (1996) exposed squirrel monkeys to high levels of Hg^0 vapors and observed a diminution in performance on lever-press behavioral responses that may reflect Hg-induced neuromotor involvement. Warfvinge (2000) also found that pregnant squirrel monkeys exposed to Hg^0 vapors at levels of 0.5–1.0 mg Hg/m^3 in air for scheduled daily periods had extensive accumulations of Hg in cerebellar nuclei, as did their offspring. In a related study, fetuses of squirrel monkeys exposed to Hg^0 vapors at levels of 0.5–1.0 mg Hg/m^3 in air daily for two-thirds of the pregnancy showed a distribution of Hg in the optic nerve, ganglion cells, and retinal pigment epithelium (Warfvinge and Bruun, 2000). A more recent study by Yoshida et al. (2002) reported that Hg^0 vapors at suprathreshold levels penetrated the placental barrier of experimental animals to intoxicate the fetal liver, kidneys, and brain, with placenta metallothionein playing a critical defensive role in the maternal to fetus transfer.

Elemental Hg vapors undergo a biotransformation in neuronal tissue the mercuric cation Hg^{2+}, which is neurotoxic. At the cellular level, Hg^0 may induce an alteration in structural proteins, enzymes, and synaptic transmitter substances. The neurotransmitter glutamate, for example, has been implicated in the neurotoxicity of I-Hg (Albrecht and Matyja, 1996; Brookes, 1992). It has been reported that Hg^{2+} selectively inhibits the uptake of synaptic glutamate in neurons of the brain, resulting in an excitotoxic elevation of glutamate in the extracellular space and associated neuronal damage (Albrecht and Matyja, 1996).

The effects of I-Hg on transduction at cellular membrane channels have been investigated through studies of Hg^{2+}. In a study on the effects of inorganic Hg on cell membranes, Liang et al. (2003) found that Hg^{2+} induced channelopathies in guinea pig sensory cells by impairing K^+ channels and changing the permeability of the cell membrane. Leong et al. (2001), for example, found that Hg^{2+} ions suppressed neuronal somata sprouting, thus inhibiting neurite growth in snails. It has been reported that inorganic and organic mercury block voltage-activated Ca^{2+} channels in nerve terminals and disrupt ligand-gated ion channels (Denny and Atchison, 1996; Sirois and Atchison, 1996). These and other experimental animal studies demonstrate a wide range of biological effects from exposure to different species of Hg (Castoldi et al., 2001; Gopal, 2003; Shafer et al., 2002; Yoshida et al., 2002).

Sources of mercury exposure in humans

Methylmercury

Mercury poisoning in children is most commonly the result of consumption of methylmercury-contaminated foods, primarily fish. Inorganic Hg deposits in aquatic environments are converted through methylation to MeHg (also called monomethylmercury) by microorganisms (bacteria, fungi, and phytoplankton) (ATSDR, 1999; Jensen and Jernelov, 1969; Wood et al., 1968). These microorganisms are consumed by other aquatic organisms, which are con-

sumed by progressively larger species. MeHg is biomagnified throughout the food chain, reaching its most toxic concentrations in the larger and long-lived predatory fish and some marine mammals that are consumed by humans. In humans, 90–100% of MeHg is absorbed through the gastrointestinal tract, where it easily enters the bloodstream and distributes throughout the body. MeHg in blood and other tissues readily binds with sulfhydryl groups, particularly the tubulin sulfhydryl groups (Castoldi et al., 2001; Kerper et al., 1992). It is transported across the blood–brain barrier by an amino acid carrier and readily accumulates in the brain (Kerper et al., 1992). MeHg also crosses the placenta and accumulates in fetal blood and brain, and in other tissues. The amount of MeHg in fetal blood is thought to be proportional to that of the mother's. The half-life of MeHg in the body is about 50 days with a range of 20–70 days, and in hair, the half-life averages about 65 days with a range of about 35–100 days (Clarkson, 1993; WHO, 1990), indicating that MeHg leaves the body slowly. The primary route of excretion of MeHg is mainly as I-Hg in feces. Although MeHg is distributed throughout all of the organs of the body, it has its most devastating effect on the developing brain. In the adult brain, MeHg damage is focal, for example, involving a loss of neurons in the visual cortex and a loss of granule neurons in the cerebellum. In the developing brain, the damage is more diffuse and extensive. MeHg affects the formation of microtubules, and thus neuronal migration and cell division (Castoldi et al., 2001; Clarkson, 1993; WHO, 1990). At high exposure levels, MeHg may result in a loss of neurons in each lobe of the brain, and the developmental effects may include hyperactive reflexes, deafness, blindness, cerebral palsy, mental retardation, and general paralysis, (Amin-Zaki et al., 1974; Bakir et al., 1973; NRC, 2000; Tsubaki and Irukayama, 1977). At low exposure levels, the neurodevelopmental effects may be subtle and include deficits in language, learning, attention, and to a lesser degree fine motor and visual–spatial organizational impairments. Several possible molecular targets of MeHg exposure in the nervous system have been presented by Castoldi et al. (2001) and include blood–brain barrier, cytoskeleton; axonal transport; neurotransmitter production, secretion, uptake and metabolism; cell signaling; protein, DNA, and RNA synthesis; and respiratory and energy-generating systems.

The serious health consequences of MeHg exposure was dramatically illustrated in 1953, when an epidemic of MeHg poisoning occurred in humans from the consumption of fish in villages around Minamata Bay, Japan (Tsubaki and Irukayama, 1977). The resulting medical disorders associated with this epidemic became known as "Minamata disease." A similar fish-mediated epidemic of MeHg poisoning occurred in riverside villages along the Agano River in Niigata, Japan, in 1964–1965 (Tsubaki and Irukayama, 1977). Another sentinel outbreak of MeHg intoxication occurred in rural Iraq in 1971–1972 from seed grain treated with a Hg-based fungicide that was to be used for planting. Unfortunately, many Iraqi farmers ground the grain into a flour and baked bread that was consumed by the local population. Tragically, more than 6500 individuals were hospitalized, and 459 died from consumption of Hg-contaminated bread. It was reported that as many as 50,000 persons may have been exposed, and neurological impairments in children were evident (Bakir et al., 1973; Myers et al., 2000; Reuhl and Chang, 1979). In both the Japan and Iraq disasters, which resulted from high-dose chronic and acute MeHg poisoning, respectively, there were many deaths, and other effects, which included mental retardation, cerebral palsy, deafness, blindness, and dysarthria, especially in children exposed in utero. Although high-dose MeHg epidemics are today uncommon, pervasive chronic low-level Hg exposure, primarily through the widespread consumption of fish, is a concern because there is evidence that low-level exposure produces subtle neurodevelopmental disabilities.

A preliminary report by the Centers for Disease Control and Prevention (CDC) of a 1999 National Health and Nutrition Examination Survey (NHANES) concluded that children younger that 5 years old in the general U.S. population have nontoxic levels of Hg, but that many women of childbearing age have Hg levels that may put the developing fetus at risk (CDC, 2001). This initial CDC study probably surveyed an insufficient number of children (n = 338) and locations (n = 12). More recently, CDC investigators examined a larger data sample from the 1999–2000 NHANES, which included 750 children (56% response rate for phlebotomy) aged 1–5 years (Schober et al., 2003), and 1709 women (74% response rate for phlebotomy) aged 16–49 years. The survey was performed in 26 locations throughout the United States. The data from the survey showed that the geometric mean total blood Hg level for the children in the sample was 0.34 μg/l (see Figs. 1 and 2). It is noteworthy that the mean blood Hg levels were significantly higher for African-Americans (Non-Hispanic

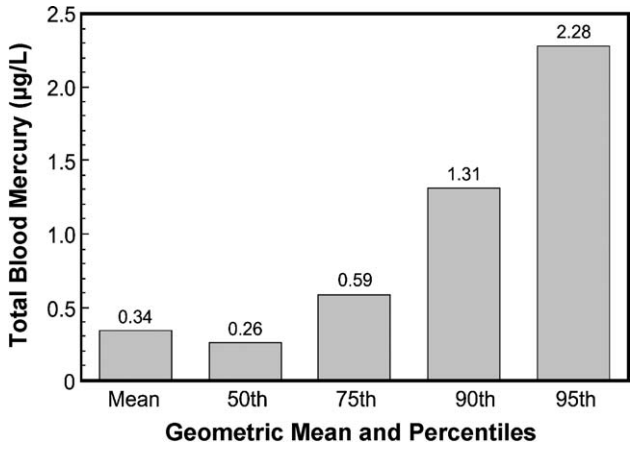

Fig. 1. Blood mercury levels for 750 children aged 1–5 years obtained during the 1999–2000 U.S. National Health and Nutrition Examination Survey (data reported by Schober et al., 2003).

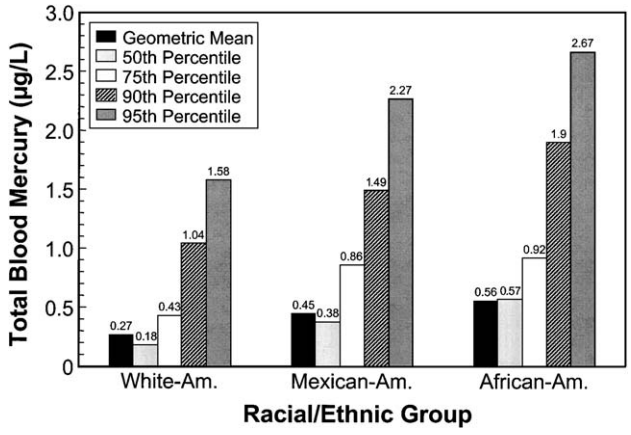

Fig. 2. Blood mercury levels for 750 children aged 1–5 years by racial/ethnic group obtained during the 1999–2000 U.S. National Health and Nutrition Examination Survey (data reported by Schober et al., 2003).

Blacks, 0.56 µg/l) and Mexican-Americans (Hispanics/Latinos, 0.45 µg/l) than European-Americans (Non-Hispanic Whites, 0.27 µg/l). Schober et al. (2003) attributed these differences to the fish species consumed, the portion size eaten, or geographic variation. The results of this survey may not be definitive, and may require a larger number of children and a more diverse survey population. For example, individuals of Asian ancestry, Native Americans, and Alaskan natives should be included in a national survey because these groups also consumed fish at levels at least equal to that of other Americans.

Following the Iraqi incident, neurodevelopmental effects of MeHg exposure have been the most widely used endpoints for assessing neurotoxic consequences of MeHg on children (National Research Council, 2000). Studies have used a variety of biomarkers, such as, the concentration of Hg in hair, maternal blood, umbilical cord blood, children's blood, children's hair, maternal fingernails, and breast milk for exposure assessment. In addition, it has been recommended that Hg levels be measured in meconium (Ramirez et al., 2000). The National Research Council (2000), however, recommends that to assess dose–response relationships, studies should assess Hg exposure by using all three of the following dose measurements: Hg in (1) maternal hair, (2) blood, and (3) cord blood. One study investigating levels of MeHg, I-Hg, and Hg^0 in pregnant and lactating women, and in the umbilical cord of the fetus, reported distinct levels of intoxication for each Hg species, with MeHg from maternal fish consumption and H^0 vapor from maternal dental amalgam fillings being the predominant exposure route to the fetus (Vahter et al., 2000).

Since the Japanese and Iraqi disasters, numerous studies have investigated the effects of chronic low-dose MeHg exposure on children using neurological and neurodevelopmental endpoints (Cordier et al., 2002; Davidson et al., 1995, 1998; Grandjean et al., 1997, 1998, 1999; McKeown-Eyssen et al., 1983; Myers et al., 1995a, 1995b, 2003). The pertinent longitudinal studies are reviewed in this section. Since the studies investigating developmental effects of MeHg exposure show disparate results, some of these studies will be reviewed in detail.

McKeown-Eyssen et al. (1983) investigated the relationship of neurological and developmental deficits to MeHg exposure from contaminated fish in 234 Northern Quebec Cree Indian children aged 12–30 months. The Hg concentrations in maternal hair segments representing prenatal exposure were used as the biomarker for Hg exposure. The mean MeHg level in hair was 6 ppm, with 6% of the maternal hair samples showing Hg levels greater than 20 ppm. A standard neurological examination and four tests from the Denver Developmental Scale (gross and fine motor function, language and personal/social skills development) were used as endpoints for exposure sequelae. The most prevalent neurological deficit was abnormal muscle tone or tendon reflexes (occurring in 14 girls and 13 boys), which was significantly associated with MeHg exposure in the boys only. An unexpected result was that the girls showed an increased probability for improved coordination with increasing Hg level. No other neurological findings were associated with MeHg exposure. No consistent dose–response relationship was observed. Because the Hg-associated abnormalities in muscle tone or reflexes were (1) of questionable clinical significance, (2) seen only in boys, and (3) showed no dose–response relationship, McKeown-Eyssen et al. (1983) concluded that their data may represent a chance occurrence. In essence, this study can be interpreted as showing no developmental effects related to MeHg for the Cree children. Nevertheless, the study by McKeown-Eyssen et al. (1983) was probably the first to suggest a gender difference related to low-dose MeHg exposure (in some of the Iraqi cases, boys were also more affected than girls). The gender effect has been inconsistently observed in later studies.

Clinical neurological outcomes of MeHg exposure were also investigated in a Peruvian population of 131 mother–child pairs in a fishing village in Mancora, Peru, between 1981 and 1984 (Marsh et al., 1995; Myers et al., 2000). The population was exposed to MeHg apparently from regular consumption of marine fish. Mean maternal hair Hg concentrations ranged from 0.9 to 28.5 ppm (geometric mean: 7 ppm), peak maternal hair levels ranged from 1.2 to 30 ppm (geometric mean: 8.3 ppm) during pregnancy. Inexplicably, the ages of the children are not listed in the published article (Marsh et al., 1995). This study showed no relationships between MeHg exposure and neurological outcomes.

Murata et al. (1999a) performed neurological, neurodevelopmental, and neurophysiological tests on 149 first graders (age range: 6.4–7.4 years) living in the settlement of Câmara de Lobos on the island of Madeira (Portugal) who were exposed to MeHg from eating fish. Mercury concentration in the children's hair was used as the biomarker for exposure, although maternal hair Hg concentration was also measured. The geometric mean hair Hg concentration for

the children was 3.82 ppm and ranged from 0.4 to 26 ppm. The scalp hair Hg levels of the mothers were higher than that of children, showing a mean of 9.64 ppm with a range of 1.1–54.5 ppm. The children were given a functional neurological examination (with emphasis on motor coordination and perceptual-motor performance) and neurodevelopmental tests, which included the following: Finger Tapping, Hand–Eye Coordination, Continuous Performance, Digit Spans, and Block Designs from the Wechsler Intelligence Scale for Children—Revised, and the Stanford–Binet Bead Memory. The study results showed no clear MeHg-associated neurodevelopmental effects on behavioral testing. Neurophysiological testing, however, showed some effects (this is discussed below).

Cordier et al. (2002) (see also Cordier et al., 1998) investigated the effects of Hg exposure on neurological and neurodevelopmental functioning in a retrospective study of 378 Amer-Indian children aged 9 months to 6 years living in different villages along the Maroni and Oyapock rivers in French Guiana. The villagers were exposed to MeHg from the consumption of fish contaminated by gold mining activities in the area. The children were divided into three groups according to their total hair Hg levels. Wayana children from the Upper Maroni River comprised the high exposure group (n = 156); Wayampi children from the Oyapock River represented the median exposure group (n = 69); and Galibi children residing on the Atlantic coast comprised the low exposure group (n = 153). Geometric mean hair Hg levels for the children were 10.2, 6.5, and 1.4 ppm for the high, median, and low exposure groups, respectively, and for the mothers 12.7, 6.7, and 2.8 ppm, respectively. Of the total group, 151 children between 9 months and 6 years were given neurological examinations, and 206 children between 5 and 12 years received neurodevelopmental tests. The results of this study showed increased deep tendon reflexes for children 2 years of age and older, which was significant in boys, but not in girls. The percentage of increased tendon reflexes for the boys grew with increasing maternal hair Hg levels: 2.6% for Hg levels less than 5 ppm, 13.2% between 5 and 10 ppm, and 27.9% for hair Hg levels above 10 ppm. The children also showed difficulty with leg coordination (measured by the McCarthy Leg Coordination test), and problems with visual–spatial organization (measured by the Stanford–Binet Copying test). No apparent overall group effects were observed for short-term memory (measured by the Stanford–Binet Bead Memory test), attention (measured by the McCarthy Digit Span test), or manual motor ability (measured by the Finger Tapping test). No major neurological deficits were found. The gender difference observed by Cordier et al. (2002) for tendon reflexes is similar to that of McKeown-Eyssen et al. (1983). However, the study by Cordier et al. is difficult to interpret because of performance differences among the three groups of children unrelated to MeHg exposure, age differences, language differences (many individuals did not speak French, apparently the native language of the investigators), and other cultural differences that hindered the investigators.

A cohort study of children in New Zealand (Kjellström et al., 1986, 1989) has been frequently referenced, but access to the report is limited, and the data have not been subjected to the kind of peer review and scrutiny as have other studies, especially the Seychelles and Faroese studies (discussed below). In the New Zealand study, exposure data (maternal hair Hg) were collected on 10,970 women in 1977 and 1978, but the study concentrated on 935 women who consumed fish more than three times per week during pregnancy. At 4 and 6–7 years of age, the children in the New Zealand study showed neurodevelopmental effects related to MeHg exposure (NRC, 2000). At 4 years of age, the significant outcomes were observed when abnormal scores on the Denver Developmental Screening Test (DDST) were combined with questionable scores. This is not standard practice for scoring the DDST, which recommends that questionable scores be combined with the normal scores. Detailed neurodevelopmental testing was performed on 237 children when they were 6–7 years old. Seventy-three children (74 mothers) whose mothers had maternal hair Hg levels greater than 6 ppm (mean: 8.3 ppm; range: 6–86; most were between 6 and 10 ppm) were classified as a high exposure group. The New Zealand study found an association between maternal hair Hg levels and full-scale IQ, language development, visual–spatial performance, and gross-motor skills (NRC, 2000).

Perhaps the most frequently cited and informative large sample epidemiological studies of the developmental neurotoxicity of MeHg are the Seychelles Child Development Study (Davidson et al., 1995, 1998; Myers et al., 1995a, 1995b) and the Faroe Islands investigations (Grandjean et al., 1997, 1998, 1999). Because these two studies are important epidemiological studies, they will be reviewed in detail.

A large prospective epidemiological study was performed by Grandjean et al. (1997) in the Faroe Islands. The Faroe Islands, which belong to Denmark, are located in the North Atlantic Ocean between Scotland and Iceland, and consist of a small Nordic community of about 45,000 inhabitants. The Faeroese are exposed to MeHg primarily through the consumption of pilot whale meat (which has a high concentration of 1.6 ppm of MeHg) and blubber (Grandjean et al., 1997). The original birth cohort of 1022 was enrolled in the study between 1986 and 1987. Fifteen percent of the mothers had hair Hg levels above 10 ppm, and cord blood Hg levels ranged as high as 350 μg/l. At 7 years of age, 917 of the original birth cohort prenatally exposed to MeHg received a functional neurological examination (with emphasis on motor coordination and perceptual-motor performance), neurophysiological testing, and an extensive neurodevelopmental test battery consisting of 11 tests (see Table 2). The neurophysiological measures included pattern reversal visual evoked potentials (VEP), brainstem auditory evoked potentials (BAER), computerized posturography (for measurement of postural sway), and

Table 2
Neurodevelopmental tests used in a longitudinal study of 7-year-old Faroese children (n = 917) prenatally exposed to methylmercury primary from the consumption of pilot whale meat

Neurodevelopmental tests	Function measured
Finger Tapping	Manual motor ability
Hand–Eye Coordination	Manual motor coordination
Tactual Performance	Tactile processing
Continuous Performance	Vigilance/attention
Wechsler Intelligence Scale for Children—Revised (three subtests)	
Digit Spans	Attention and tracking
Similarities	Reasoning and cognitive flexibility
Block Designs	Visual–spatial organization and reasoning
Bender Gestalt	Visual–spatial/right cerebral hemisphere
California Verbal Learning	Short-term memory
Boston Naming	Language (word retrieval)
Nonverbal Analogue Profile of Mood States	Experimental measure of mood

Grandjean et al. (1997).

electrocardiography (to indicate autonomic nervous system function). Each child underwent 5 h of testing. Cord blood Hg level was used as the primary indicator of MeHg exposure, which Grandjean et al. (1997) believe to be the best predictor of neurodevelopmental disorders related to Hg exposure. The geometric mean cord blood Hg concentration for the children was 22.8 μg/l. The primary results from this study revealed that MeHg exposure was associated with deficits in attention, language, and memory, and to a lesser degree with decreased performance in visual–spatial and motor skills. The functional neurological examination did not yield any unequivocal dysfunctions associated with Hg, but there were some suggestive neurophysiological abnormalities in the BAERs.

Neurophysiological endpoints, such as BAERs and VEPs have also been used in other studies in an effort to utilize objective physiological measures that are less affected by social confounders. The findings from the Grandjean et al. (1997) study for pattern reversal VEPs revealed no significant association with cord Hg concentration in 7-year-old children (n = 813) from the Faroe Islands cohort. The BAERs results were, however, suggestive of an association. According to Grandjean et al. (1997), the results on 824 children (aged 7 years) indicated that BAER peak latencies for waves III and V were significantly associated with Hg exposure (the authors' Table 3, however, shows a P value of 0.06 for peak III). The BAER interpeak latencies showed no correlation with Hg exposure, and the pure-tone thresholds were not significantly associated with MeHg exposure (Grandjean et al., 1997). The absence of any exposure-associated increase in BAER interpeak latencies suggests that the Hg exposure at the concentration levels of the children in the Faroe Islands study had no significant effect on auditory brainstem neural conduction. It is logical, however, to expect more of an association with the BAER interpeak latencies, which reflect the conduction capacity of central neurons, than the absolute latencies, considering the affinity of MeHg for the brain. On the other hand, the increased latency for the BAER waves III and V could be consistent with a subtle hearing loss (some studies suggest that Hg impairs high-frequency hearing; Counter et al., 1998; Rice and Gilbert, 1992). In a later study, the Faroe Islands group (Murata et al., 1999a) also investigated the effects of MeHg on BAERs and VEPs in 149 children from the Island of Madeira. As indicated above, the hair Hg concentration for the children ranged from 0.4 to 26 ppm. The neurophysiological data revealed increased latency for peak III of the BAERs, and for N145 on the pattern-reversal VEPs when maternal hair Hg level exceeded 10 ppm. In light of the findings in this study, the Faroe Islands group (Murata et al., 1999b) reanalyzed the neurophysiological data from their 1997 research report (Grandjean et al., 1997). The rationale given for reanalyzing the data was test equipment changes between 1993 and 1994 (when the data reported in 1997 were collected). The BAER latencies were shorter and VEP latencies were longer in 1994. The reanalysis involved only the 1993 data, and showed significant association of BAER latencies for wave III and interpeak intervals I–III with maternal hair Hg (range: 0.6–39.1 μg/l; geometric mean: 4.49 μg/l) and cord blood Hg (range: 3.3–351 μg/l; geometric mean: 23 μg/l), but not with the children's own hair Hg level (range: 0.04–26.4 μg/l; geometric mean: 3.42). The VEPs were not associated with any of the Hg biomarkers. A study by Counter et al. (1998), in which BAER data were obtained on 19 children and adults in the Nambija gold mining area of Ecuador (mean blood Hg levels: 20.6 μg/l; range: 7–45 μg/l), showed an association of the BAER I–III interpeak latency on the left side with blood Hg level. In a more recent study, Counter (2003) measured BAERs in 31 children (aged 4–14 years) with a mean blood Hg level of 23 μg/l (range: 2–89 μg/l). The results showed associations among BAER interpeak latencies of I–V, III–V, I–VI, and absolute latencies of waves V and VI for Hg levels higher than 20 μg/l. In general, these studies suggest that neurophysiological endpoints, such as BAERs and VEPs, may be useful in assessing the neurodevelopmental consequences of Hg exposure. This area of research merits further study, particularly because neurophysiological measures are generally not affected by the many socioeconomic and cultural confounding variables that are inherent in neurobehavioral testing.

The U. S. National Academy of Sciences (NRC, 2000) used the Faroe Islands study as the critical study for recommending a scientifically based reference dose (RfD) for MeHg exposure. One of the confounding factors in the Faroe Islands study is that the inhabitants of the Faroe Islands are also exposed to high levels of polychlorinated biphenyls (PCB), which may also be associated with neurodevelopmental effects (Jacobson and Jacobson, 1997; Rogan and Gladen, 1991, 1992; Rogan et al., 1986; Stewart et al., 2003). Based on its review of published studies, the

National Academy of Sciences (NRC, 2000) concluded that the adverse outcomes observed in the study were not due to PCB exposure. However, Stewart et al. (2003) suggested that in the Faroe Islands study, there might have been a PCB–MeHg interaction. Stewart et al. (2003) investigated cognitive functioning in 212 PCB-exposed children in Oswego, NY, who also were exposed to very low levels of MeHg (indicator medium: maternal hair). Their results showed that elevated PCB levels enhanced the association between MeHg and McCarthy scales performance, suggesting a potentiation of MeHg neurodevelopmental effects by PCBs. Further research is needed before firm conclusions can be made about PCBs–MeHg interaction and developmental outcomes.

The positive findings in the Faroe Islands study were in contrast to the results of a similar epidemiological study performed in the Republic of Seychelles (Davidson et al., 1995, 1998; Myers et al., 1995a, 1995b). The islands of Seychelles are located about 1000 miles (1600 km) east of the African mainland. Over 90% of the population lives on the main island of Mahe, and healthcare, preventative health services, and educational services are reported to be of high quality. There is no local pollution, and maternal use of alcohol and tobacco is low (Myers et al., 2000). French, English, and Creole are spoken in the Republic of Seychelles. MeHg exposure in this population occurs from the consumption of fish (85% of the population eats marine fish daily) (Davidson et al., 1998). The children in the Seychelles Child Development Study (SCDS) have been evaluated using neurodevelopmental endpoints at 6, 19, and 29 months of age with no adverse outcomes related to MeHg exposure (Davidson et al., 1995; Myers et al., 1995a, 1995b). Of the 779 mother–child pairs originally recruited for the SCDS, 711 were reevaluated when the children were 66 months (5.5 years; ±6 months) of age (Davidson et al., 1998). The total Hg concentration in a section of maternal hair representing growth during pregnancy was used as the biological indicator for prenatal exposure. Postnatal exposure was assessed by obtaining total Hg concentration in a 1-cm segment of hair near the scalp of the children at 66 months of age (in 25 children, hair samples were obtained at 48 months because in these children, the samples were inadequate for analysis at 66 months). Mean maternal hair total Hg during pregnancy was 6.8 ppm (SD: 4.5; range: 0.5–26.7), and mean child hair total Hg level at 66 months was 6.5 ppm (SD: 3.3; range: 0.9–25.8). According to the authors, these levels are typical of communities in which fish is a major part of the diet (during enrollments in the study, the mothers reported eating about 12 fish meals a week). An analysis of 350 samples of fish from 25 different species revealed median Hg concentrations that ranged from 0.05 to 0.25 ppm, which the authors indicated are comparable with fish in the United States. The six neurodevelopmental tests used in this study are presented in Table 3. Hearing was evaluated by obtaining pure-tone thresholds, apparently to rule out neurodevelopmental effects related to hearing loss. All tests were given in Creole because 98% of Seychellois speak Creole at home (Davidson et al., 1998). No adverse developmental effects were found in this study. These results were consistent with the authors' earlier studies. Davidson et al. (1998) concluded that a high fish diet did not seem to put the Seychellois children at risk for compromised developmental outcomes. In another fish-consuming population study by Evens et al. (2001), it was reported that despite moderate dietary intake of fish and seafood, children in Casa Pia, Portugal, had blood MeHg levels less than those found in studies in which significant neurobehavioral effects were suggested.

Table 3
Neurodevelopmental tests used to evaluated 5.5-year-old children in the longitudinal Seychelles Child Development Study (n = 711) prenatally exposed to methylmercury from the consumption of fish

Neurodevelopmental tests	Function measured
General Cognitive Index of the McCarthy Scales for Children's Abilities	cognitive ability
Preschool Language Scale	expressive and receptive language abilities
Woodcock–John Tests of Achievement	
Letter and Word Recognition	reading achievement
Applied Problems	arithmetic achievement
Bender Gestalt	visual–spatial ability
Child Behavior Checklist (total T score)	social and adaptive behavior

Davidson et al. (1998).

A group of 643 children from the original cohort of 779 children in the Seychelles study were recently examined in a follow-up study at 9 years of age (Myers et al., 2003). In this study, the investigators included a wide range of both global and domain-specific measures, including tests used in other studies and those that are apparently sensitive to the effects of MeHg exposure. Twenty-one neurodevelopmental endpoints were assessed (see Table 4), and testing required 3 h. The mean age at the time of testing for the children was 107 months. Audiologic testing (audiometry and tympanometry) was performed, apparently to rule out hearing loss. Of the 21 neurodevelopmental endpoints, only two were associated with MeHg exposure: performance on the Grooved Pegboard and the Conner's Teacher Rating Scale. However, the Grooved Pegboard showed an adverse relationship only with the nondominant hand in boys. The Conner's Teacher Rating Scale showed improved scores on the hyperactivity index. Myers et al. (2003) concluded that these were probably chance findings.

Ethylmercury

In recent years, there has been concern that ethylmercury exposure may induce neurodevelopmental disabilities, such as language delay, attention deficit-hyperactivity disorder, but especially autism spectrum disorder (Geier and Geier, 2003). Ethylmercury (EtHg) is an organic Hg compound, and in the form of thimerosal has been used as a topical antiseptic and as a preservative in vaccines routinely given

Table 4
Neurodevelopmental tests used in a longitudinal study of 9-year-old Seychelles children (n = 643) prenatally exposed to methylmercury from the consumption of ocean fish

Neurodevelopmental tests	Function measured
Finger Tapping	motor function
Trailmaking	motor function
Grooved Pegboard	motor function
Bruininks–Oseretsky	motor proficiency
Haptic Matching	
Connor's Continuous Performance	sustained attention
Wechsler Intelligence Scale for Children—III (13 subtests)	
Full Scale IQ	intelligence
Berry–Buktenica	visual–motor integration
California Verbal Learning	learning and achievement
Boston Naming	language (word retrieval)
Woodcock–Johnson (two subtests)	learning and achievement
Letter–Word Recognition	reading
Applied Problems	
Connor's Teacher Rating Scale	behavior

Myers et al. (2003).

to children, including diptheria-tetanus-acellular pertussis (DTP), hepatitis B, and some *Haemophilus influenzae* type b (Goldman and Shannon, 2001; Halsey, 1999; Pichichero et al., 2002). Thimerosal contains 49.6% Hg by weight and is metabolized to EtHg and thiosalicylate. The normal dose of a pediatric vaccine contains about 12.5–25 μg of Hg per 0.5 ml (American Academy of Pediatrics, 1999). In some cases, when vaccines containing thimerosal have been given at their recommended doses, local hypersensitivity reaction has been observed, but no other adverse effects have been seen (American Academy of Pediatrics, 1999; Ball et al., 2001). The EPA rapidly responded to the concerns about thimerosal in vaccines because of the possibility that some infants who receive multiple doses of thimerosal-containing vaccines could exceed federal guidelines. In July 1999, the EPA requested plans from vaccine manufacturers about removing thimerosal from vaccines (American Academy of Pediatrics, 1999). Thimerosal has been removed from most vaccines in the United States, but is still used in vaccines in some developing countries.

The adverse effects of high-dose EtHg are thought to be similar to those of high-dose MeHg (Ball et al., 2001; Halsey, 1999), but the effects of low-dose EtHg are unclear. As mentioned previously, the transport of MeHg across the blood–brain barrier is facilitated by an amino acid transport system. Ethylmercury, however, is not thought to have such an active transmission mechanism. In addition, EtHg has a larger molecular size and decomposes at a faster rate than MeHg (Kerper et al., 1992; Magos, 2003). A review by Magos (2001) of 18 cases (six of whom were children) of EtHg poisoning suggests that EtHg may be less toxic neurologically than MeHg. In five of the cases (all adults) whose blood Hg levels varied from 0.11 to 0.65 Hg/ml (110 to 650 μg/l), no effects were observed. Magos (2001) concluded that EtHg may begin to present a risk at blood levels of 1 μg Hg/ml (1000 μg/l), and that severe poisoning may occur at 2 μg Hg/ml (2000 μg/l). These risk levels are much higher than MeHg risk levels, and if correct suggests that EtHg may not be as toxic as MeHg. In an experimental study using cortical human neurons, Baskin et al. (2003) found that thimerosal in micromolar concentrations changes cell membrane permeability and induced DNA breaks and apoptosis.

Pichichero et al. (2002) determined the concentration of Hg in blood, urine, and stools of infants who received vaccines containing thimerosal. Sixty-one full-term infants aged 2 and 6 months were recruited for the study. Forty of the sixty-one infants were given vaccines that contained thimerosal, and 21 received thimerosal-free vaccines. The study results indicated low Hg levels in the blood of the infants, ranging from 3.7 to 20.5 ppb in 2-month-old infants, and less than 7.5 ppb in all 6-month-old infants. The estimated half-life of Hg in the blood was 7 days, being eliminated from the body rapidly through the stools. It is unclear if the Hg levels in the blood of the infants would have been higher had the blood samples been taken shortly after vaccination (e.g., within 72 h) instead of the 3–28 days reported by Pichichero et al. (2002). It does seem clear, however, that thimerosal-containing vaccines increase the level of Hg in the blood of infants. For example, Stajich et al. (2000) found that following a dose of thimerosal-containing hepatitis B vaccine, prevaccination blood Hg levels increased from 0.54 to 7.36 μg/l in 15 preterm infants, and from 0.04 to 2.24 μg/l in 5 term infants. Although the blood Hg levels after a single dose of thimerosal-containing vaccine are low, the rationale for removing thimerosal from vaccines is that children who are given multiple doses of thimerosal-containing vaccines run the risk of exceeding the EPA's RfD through cumulative exposure.

Bernard et al. (2001) hypothesized that autism spectrum disorder is a mercurial syndrome. Autism spectrum disorder is characterized by impairment in social interaction, communication, and behavior (American Psychiatric Association, 1994). Some of the specific aspects of the disorder consist of repetitive motor behaviors (stereotypies), speech delay and speech echolalia, hypersensitivity to sensory stimuli, socially aloof behavior, and an insistence on sameness (Nelson and Bauman, 2003). The child may have normal developmental milestones during the first or even second year of life when developmental regression sets in. In a review comparing the neuropathology of autism with that of Hg poisoning, Nelson and Bauman (2003) concluded that there is a major difference in the neuropathologic findings in autism compared to Hg intoxication, and that there is no other evidence to support the hypothesis advanced by Bernard et al. (2001). In a review of the literature, Ball et al. (2001) concluded that there was no evidence of adverse effects induced by thimerosal in vaccines, except for the well-known hypersensitivity response.

Recently, Geier and Geier (2003) performed an analysis of the Vaccine Adverse Events Reporting System (VAERS)

database and compared the incidence of neurodevelopmental disorders for thimerosal-containing DTaP (diphtheria, tetanus and acellular pertussis) and thimerosal-free DTaP vaccines. The authors were specifically concerned with the incidence of autism, speech disorders, and mental retardation. From their analysis of the VAERS database, Geier and Geier (2003) determine that there were 6575 adverse reaction reports for thimerosal-containing DTaP vaccines, and 1516 adverse reaction reports for thimerosal-free DTaP vaccines. The authors further reported that there were statistically significant increases in the incidence of autism, mental retardation, and speech disorders for the thimerosal-containing DTaP vaccine cases, compared to thimerosal-free DTaP vaccine cases. The relative risk (incidence of adverse reactions to thimerosal-containing vaccines divided by the incidence of adverse reactions to thimerosal-free vaccines) was 6.1 for mental retardation, 6.0 for autism, and 2.2 for speech disorders. Geier and Geier (2003) concluded that children who receive 75–100 μg of thimerosal from thimerosal-containing DTaP vaccines may have an increase in neurodevelopmental disorders. The data from the Geier and Geier (2003) study should be interpreted with caution because the VAERS database, established by the U.S. Food and Drug Administration, is a passive surveillance system for clinical consequences apparently related to immunization (Braun et al., 2000; Kimmel, 2002). That is, the VAERS database has inherent limitations because: (1) it is a passive surveillance system in which different health professionals, state health organizations, manufacturers, and parents submit reports; (2) it does not have consistent diagnostic criteria; and (3) it is prone to underreporting (Ball et al., 2001; Kimmel, 2002).

Recent population-based studies (Hviid et al., 2003; Madsen et al., 2003; Stehr-Green et al., 2003) analyzing data on the prevalence of autism in Sweden and Denmark, where thimerosal was eliminated from vaccines in 1992, do not support a causal association between thimerosal-containing vaccines and the apparent increased incidence of autism. That is, in both Sweden and Denmark, the incidence of autism spectrum disorders continued to increased well beyond 1992 (when thimerosal was eliminated from vaccines) into 1999–2000. A recent two-phase retrospective cohort study investigated the relative risks of neurodevelopmental disorders from cumulative exposure to thimerosal-containing vaccines (Verstraeten et al., 2003). The study consisted of an analysis of computerized databases from two HMOs in phase I, and an analysis of data from an additional HMO in phase II. Phase I consisted of the analysis of data for 124,170 infants born during 1992–1999, and Phase II consisted of the analysis of the records of 16,717 children born during 1991–1997. In phase I, significant positive associations were found for thimerosal and tics and language delay, but during phase II, no significant associations were found. For either phase of the study, no significant associations were found for autism or attention-deficit disorder. Verstraeten et al. (2003) concluded that there were no clear associations between thimerosal exposure in infant vaccines and neurodevelopmental outcomes. Because of noted inconsistencies among the HMO databases, Verstraeten et al. (2004) recommended that studies with comparable neurodevelopmental evaluations of children with a range of thimerosal exposures be performed for more definitive conclusions. In summary, currently, there appears to be no substantial evidence that EtHg in the amounts contained in vaccines is associated with neurodevelopmental disorders, including autism spectrum disorder.

Elemental mercury

Elemental mercury (Hg^0) is a naturally occurring metal (commonly called quicksilver) that exists uniquely in liquid form at room temperature and quickly turns to vapor when heated. It has a vapor pressure of 0.0007775 mm at 10 °C, which increases exponentially as the temperature is doubled. The natural sources of Hg^0 in the environment include the release of Hg gases from volcanic eruptions and the erosion of ores that contain Hg. Sources of Hg^0 exposure from human enterprise include industrial fossil fuel emissions, topical medicines, cathartics, dental amalgam, thermometers, sphygmomanometer, barometers, incandescent lights, batteries, medical waste incineration, and Hg-based substances used in ritualistic practices (American Family Physician, 1992; Cranmer et al., 1996; Goldman and Shannon, 2001; Hudson et al., 1987; Isselbacher et al., 1994; Vroom and Greer, 1972; WHO, 1991). The toxicological effects of Hg^0 are summarized in Table 1.

Elemental Hg is more hazardous to humans in the vaporized state. The toxic effects of Hg^0 vapors in humans have been known for centuries, especially in association with occupational endeavors. Reports of Hg^0 intoxication have been traced back to the writings of Hippocrates and Galen, and in western clinical literature to Ulrich Ellenbog in 1524 (Goldwater, 1957). The occupational use of Hg^0 in Japan was reported as early as the eighth century (Satoh, 2000). Because children were often a source of labor in early large and small cottage industries in both Eastern and Western societies of past centuries, it is likely that Hg^0 exposure was equally common among children and adults of earlier periods. In the early 20th century, systematic and well-documented clinical and scientific reports of the effects of exposure to Hg^0 vapors appeared in the literature. However, most early clinical reports of Hg^0 intoxication typically involved adults with occupational exposure to Hg vapors or dust (Malm, 1998; Ratcliffe et al., 1996; Sweet and Zelikoff, 2001; Vroom and Greer, 1972; WHO, 1991; Williams and Schram, 1937).

Exposure to toxic Hg^0 vapors may be acute or chronic, occupational or residential. Inhalation of Hg^0 vapors in concentrations greater than 0.05 mg/m^3 for significant periods is considered unsafe by the ATSDR (1992). The minimum risk level from chronic Hg^0 inhalation is 0.3 $\mu g/m^3$. Both acute and chronic Hg^0 exposure may induce a

broad sequelae of reactions or symptoms, including cough, dyspnea, fever, tremors, malaise, axonal sensorimotor polyneuropathy, gingivitis, delusions, hallucinations, and mercurial erethism, a syndrome that includes excitability, loss of memory, insomnia, extreme shyness, and neurocognitive disorders. Children exposed to Hg^0 vapors may exhibit many of the above symptoms, as well as breathing difficulty, swelling and erythema of the hands and feet, and pealing pink skin at the tips of the fingers and toes, symptoms collectively called acrodynia (Albers et al., 1982; ATSDR, 1992, 1999; CDC, 1991; Clarkson, 2002; Isselbacher et al., 1994; Satoh, 2000).

More than 80% of inhaled Hg^0 vapor is absorbed by the lungs. Elemental Hg diffuses across the membranes of the alveolar sacs and enters the blood to bind with red blood cells in body tissues where it oxidizes to form mercuric ions ($Hg^0 \rightarrow Hg_2^{2+} \rightarrow Hg^{2+}$) and binds with the sulfhydryl groups. Oxidized Hg^0 is accumulated in the brain, liver, and cortex of the kidneys. The biotransformation of highly lipid soluble Hg vapor to mercuric Hg in the brain may lead to an accumulation of Hg^{2+} in the cortex and cerebellum, producing impairment of the CNS. Measures of the half-life of mercury involve a two-compartment system, consisting of a short half-life and a longer half-life component. The half-life of inhaled Hg^0 is 60 days (range 31–100 days), with most being eliminated through urine and fecal excretion. A small amount of absorbed Hg^0 is eliminated through exhalation, sweat, and saliva (ATSDR, 1992; Goldman and Shannon, 2001; Halbach and Clarkson, 1978; Houeto et al., 1994).

Elemental Hg intoxication in children may result from: (1) inhalation of Hg vapors, (2) exposure to Hg dust and powders, (3) exposure to latex paint containing a Hg-based fungicide, (4) accidental ingestion of Hg from instruments, such as thermometers, and (5) dental amalgams (Samuels et al., 1982; ATSDR, 1999; Evens et al., 2001; Pesch et al., 2002; Björnberg et al., 2003). Children are believed to be at higher risk for Hg^0 vapor inhalation in residential settings because the Hg vapor settles on the floor, which is in closer proximity to the crawling infant or walking toddler's respiratory system. In addition, children may handle, play with, or ingest the curiously shiny liquid Hg^0 (although only about 0.01% of Hg^0 is absorbed from the gastrointestinal tract) or Hg powders.

Pediatric Hg^0 exposure is uncommon in most developed countries today and typically occurs only by accident. The medical literature on the toxicological effects of Hg^0 exposure in children contains several references to single, isolated accidental Hg^0 exposure cases, but large cohort studies are rare. However, some recent studies have reported an increase in Hg^0 exposure among urban children who are exposed to vaporized Hg-based powders and metallic Hg used within their homes for ritualistic-spiritual purposes (Forman et al., 2000; Riley et al., 2001). In many gold mining operations of the Amazon Basin, the burning of gold amalgams in the outdoors by gold miners or indoors by miners' families and gold jewelry makers has been found to be a source of toxic Hg^0 exposure (Malm, 1998). Some studies show evidence of increasing pediatric Hg intoxication among certain indigenous Amer-Indians from exposure to Hg^0 vapors inhaled during the burning of mercury–gold amalgam by their parents in the gold mining activities (Counter, 2003; Counter et al., 1998, 2002). In fact, the widespread use of Hg in amalgam by families to extract gold from ore may have increased pediatric Hg vapor exposure worldwide (Snodgrass et al., 1981; Solis et al., 2000; Soni et al., 1992).

Pulmonary dysfunction is the primary cause of mortality in children who inhale high levels of toxic Hg^0 vapors. For example, Campbell (1948) reported a detailed case of acute pediatric Hg intoxication and death in a 4-month-old following exposure to evaporated metallic Hg vapors from a hot stove in an unventilated apartment. An autopsy revealed pulmonary edema, general edema, nephrotic degeneration, ventricular dilation, and a greyish, necrotic appearance in the mucosa of the stomach and duodenum. Matthes et al. (1958) reported the clinical course and eventual deaths of three children aged 4, 20, and 30 months from acute Hg^0 vapor exposure in the home. The primary pathological findings in the three children were severe interstitial pneumonitis, erosion of the bronchial epithelium, membrane lesions of the alveoli, and alveolar ducts and significantly elevated Hg in the kidneys and liver. Moutinho et al. (1981) likewise reported a fatal case of accidental Hg^0 vapor inhalation in a 7-month-old infant within the home during the melting of metallic Hg by the father in the family kitchen. The infant exhibited dyspnea and eventual apnea over a period of 7 days, rapidly followed by the bilateral collapse of portions of the lungs, severe acidosis, coma, seizures, and death. A postmortem examination revealed severe damage in all five lobes of the lungs, including edema, desquamation of the cells lining the alveoli and alveolar ducts, and degeneration in renal tubular cells. It is also significant that the family's 6-month-old cat was simultaneously exposed to the Hg^0 vapors and died within hours of the initial exposure. A postmortem on the cat revealed diffuse pneumonitis and pleural effusions, suggesting respiratory failure (Moutinho et al., 1981).

During pregnancy, inhaled Hg^0 vapors absorbed by the mother's tissues may diffuse across the placenta to accumulate in the fetal brain and induce neurodevelopmental anomalies. For example, Lien et al. (1983) reported elevated blood Hg in three children and a pregnant woman who were accidentally exposed to Hg^0 vapors. They found that the blood Hg of the mother and newborn were similar, suggesting direct transfer across the placenta. Impaired gait, numbness in fingers and toes, absence of deep tendon reflexes, elevated blood pressure, and elevated protein in the cerebrospinal fluid were observed in two children exposed to an Hg^0 spill of 20 cm^3 with indoor air Hg concentrations of 10–40 $\mu g/m^3$ in the home (CDC, 1991). Acute cerebellar ataxia, anorexia, fatigue, weakness, and back pain were reported in children (siblings) exposed to vapors from

spilled elemental Hg in their residence (Florentine and Sanfilippo, 1991). Soni et al. (1992) reported acute Hg^0 vapor intoxication in a 3-year-old boy and the death of a second child exposed to the heating of Hg by the parents during a Hg amalgamation–gold extraction process. Solis et al. (2000) reported the death of a 13-month-old boy from acute exposure to Hg^0 vapors during his parents' use of liquid Hg to extract gold from ore in a poorly ventilated kitchen. The infant had respiratory failure within 24–36 h after admission and died 25 days later showing a cellular filtrate in the alveolar sacs and severe pneumonitis. Other children in the household were similarly intoxicated by the Hg vapors (estimated at a concentration of 0.193 mg/m^3 in air) but were treated successfully with chelation therapy (Solis et al., 2000).

Cherry et al. (2002) reported long-term exposure to Hg^0 vapors from a Hg spill in a family residence. Over a period of 6 months of exposure to Hg vapor, a 3-year-old child in the household presented with progressive weight loss, irritability, tremors, abnormal EEG, loss of speech and language, and ataxia. In one study of 23 children of thermometer plant workers and 39 children in a reference (control) group, higher urine Hg levels were found in the study group and higher Hg-in-air levels were measured in the homes of the thermometer plant workers than in the homes of the reference group (Hudson et al., 1987). This study demonstrated the risk of Hg intoxication for families of workers who are exposed to Hg in the workplace and who may inadvertently transport the toxic Hg to their homes via their clothing and shoes. Many states and cities in the United States have banned the manufacture and sale of Hg-filled thermometers.

In recent years, a novel type of Hg^0 poisoning in children has been reported with increased frequency in American medical literature. For example, Forman et al. (2000) investigated nine children in one family that had been exposed to Hg^0 vapors from spilled Hg-filled amulets purportedly used in the Afro-Caribbean religion, Santeria. They found highly elevated pretreatment Hg levels in urine, which they reduced therapeutically with a succimer (DMSA) treatment regimen (Forman et al., 2000; Miller, 1998). Several earlier studies reported evidence of the use of Hg-filled capsules and beads in magico-religious rituals by urban American minorities (Riley et al., 2001; Wendroff, 1995; Zayas and Ozuah, 1996). As part of the rituals, Hg-based powders are regularly sprinkled about the home where the Hg^0 vaporizes and is inhaled as Hg vapor by the residents, particularly the small children who are more commonly at floor level where the Hg^0 vapors settle. Ozuah et al. (2003) conducted a 3-month clinical investigation of the prevalence of Hg exposure in 100 urban, largely Hispanic and African-American children and found that 5% had elevated urinary Hg levels. They suggested that the elevated mercury levels in these children may have resulted from exposure to Hg-filled capsules purchased locally from "Botanicas," mainly by women for magico-religious purposes. This is a widening health hazard in some urban minority communities and requires increased public health attention. The situation also requires improved education regarding the health risks of Hg for the exposed population, and additional cultural education for the physicians and other caregivers to increase their sensitivity and awareness of this mode of Hg exposure.

Inorganic mercury compounds

Inorganic Hg (I-Hg) compounds (mercury salts) are also a significant source of Hg intoxication in both adults and children in some countries. The toxicological effects of I-Hg are summarized in Table 1. Inorganic Hg compounds have been used for many years in numerous products, including various medications, germicidal soaps, teething powders, and skin creams. Many of these Hg-based products are still in use today (Goldman and Shannon, 2001). Some skin creams, for example, contain as much as 6–10% mercurous chloride (HgCl) or "calomel." For many years, a mercurous chloride "calomel" (also known as sweet mercury) was used in infant teething powders as an analgesic (American Family Physician, 1992; ATSDR, 1999; Isselbacher et al., 1994). As with other forms of Hg poisoning, inorganic mercurial preparations may induce fatigue, insomnia, weight loss, paresthesias of the feet and hands, erythema, pruritus, excessive perspiration and hypersalivation, progressive weakness in the extremities, renal tubular dysfunction, and neuropsychiatric disorders (Dyall-Smith and Scurry, 1990; Weldon et al., 2000).

An example of severe I-Hg poisoning in children was reported by Weinstein and Bernstein (2003) in 20-month-old twin girls who had been administered a Hg-based teething powder for 4 months. The infants presented with pain in the extremities, papular rash, weakness, anorexia, and acrodynia. In adults, I-Hg poisoning most commonly results from cutaneous application of Hg-based soaps and creams known as bleaching or skin-lightening creams (Adebajo, 2002; Al-Saleh and Al-Doush, 1997; Al-Saleh and Shinwari, 1997; del Giudice and Yves, 2002; Garza-Ocanas et al., 1997; Goldman and Shannon, 2001; McRill et al., 2000; Soo et al., 2003; Tlacuilo-Parra et al., 2001). The mercurous chloride in such "beauty creams" as Crema de Belleza-Manning is readily absorbed through the skin and may produce chronic Hg intoxication and associated clinical disorders (Palmer et al., 2000; Tlacuilo-Parra et al., 2001).

Some studies show that the majority of persons using skin-lightening chemicals are female, and some use skin lighteners to attain a higher social status. Many of the women who use Hg-based skin-lightening creams are of childbearing age, a fact that may have serious implications for the possible transfer of Hg from mother to fetus (CDC, 1996a, 1996b; del Giudice and Yves, 2002; Dyall-Smith and Scurry, 1990; Weldon et al., 2000). Particularly alarming is the evidence that exposure to the I-Hg salts in the skin lighteners may impair the

developing fetus (Lauwerys et al., 1987). Women of childbearing age who use Hg-based skin whiteners may place their unborn fetus at risk for neurological, nephrological, and dermatological disorders.

Dyall-Smith and Scurry (1990) reported elevated levels of Hg in blood and urine, facial mercury pigmentation changes, and possible neuropsychiatric involvement in a woman who regularly used a 17.5% mercuric ammonium chloride-based cream to lighten her complexion. In another study, Garza-Ocanas et al. (1997) found high urinary Hg levels and associated tremors and exanthem in a woman with cutaneous 5.9% HgCl (calomel) exposure from long-term use of a whitening facial cream. Weldon et al. (2000), for example, found increased urine concentrations of Hg in a group of women on the Mexican–U.S. border who regularly applied the widely used skin whitener, Crema de Belleza-Manning to their skin. The same study reported a urine Hg level of 178 μg/l in an adolescent who regularly used the skin-lightening cream. Similarly, Tlacuilo-Parra et al. (2001) found malar rash, facial sensitivity in sunlight, weakness, erythema, and a constellation of neurological symptoms in a woman of childbearing age who had used Crema de Belleza-Manning daily for about 5 years. del Giudice and Yves (2002) found extensive use of skin-lightening creams with associated adverse cutaneous effects in Senegalese women and concluded that the use of such toxic creams is widespread in Sub-Saharan Africa. Soo et al. (2003) reported a case of an Indonesian woman with nephrotic syndrome secondary to membraneous nephropathy and a urine Hg level 2000 times higher than normal from the use of a Hg containing "skin-whitening cream."

Reports of Hg poisoning from exposure to skin-whitening creams, ointments, and soaps have increased dramatically in recent years. Further, because children with lighter skins may represent a higher status in some cultures, skin-whitening cosmetics may be applied to children by their parents to enhance their appeal and currency (Jovanovic et al., 1997; Otto et al., 1994; Weldon et al., 2000). Otto et al. (1994), for example, found high Hg concentrations in the blood and urine of Balkan refugees of different ages who had been exposed to a Hg-based skin "bleaching ointment." The potential developmental effects of prenatal I-Hg exposure in children born to mothers who have used Hg-based creams and soaps during pregnancy is a subject in need of further scientific investigations. Further, the effects of postnatal cutaneous exposure to I-Hg from skin-lightening creams and soaps applied to children by their parents are in need of further study.

Elemental and inorganic mercury exposure from dental amalgams

An elevated level of Hg in the blood and tissue of the fetus and infant from any source is a potential cause of neurodevelopmental disabilities. It has been known for sometime that dental amalgam is a major source of Hg^0 exposure in humans because Hg is the principal metal in most dental fillings (approximately 50% Hg by weight) (Nadarajah et al., 1996). The health effects of dental amalgam Hg have been a subject of considerable debate for years, with no scientific consensus on an association between amalgam Hg exposure and adverse health consequences, either in adults or children (Clarkson, 2002; Ratcliffe et al., 1996). However, questions have been raised regarding a possible association between maternal Hg dental fillings and the health of the developing fetus, neonate, and infant. Significant levels of Hg have been measured in oral vapor, blood, and in organs of animals and humans with Hg-containing dental amalgam restorations (Abraham et al., 1984; Snapp et al., 1989; Vimy et al., 1990, 1997). In the oral cavity, Hg^0 vapor is rapidly oxidized to inorganic divalent Hg (Hg^{2+}) in vivo after release from dental amalgam and absorbed through inhalation. Experimental animal studies have shown that Hg released from amalgam restorations crosses the placenta and induces an increase of Hg concentration in the blood, liver, and kidney of the fetus (Takahashi et al., 2001, 2003; Vimy et al., 1997). Vimy et al. (1990), for example, in a study using sheep with implanted amalgam fillings, reported positive correlations between increased concentrations of Hg in breast milk, urine, and oral vapor with the number of maternal amalgam fillings.

In humans, Drasch et al. (1994) found significant positive correlations between I-Hg concentrations in the liver and kidneys of both fetuses and infants and the number of maternal teeth with amalgam fillings. They also reported that maternal fillings may influence the concentration of Hg in the cortex of older children. Oskarsson et al. (1996) reported significant correlations between Hg levels in blood and the breast milk of lactating women as a result of absorption from dental amalgam fillings. Similarly, Vahter et al. (2000) found that the concentration of I-Hg in the fetus is influenced by the number of maternal dental amalgam fillings. Ask et al. (2002) reported that the median concentration of I-Hg in the placenta was four times higher than in maternal and umbilical cord blood, and that the accumulation of placental Hg was influenced by the number of maternal amalgam fillings. They concluded that the high I-Hg concentration observed in the placenta originated from Hg^0 released from Hg amalgam fillings and oxidized to Hg^{2+} by catalase in the blood. Pesch et al. (2002) examined German children with amalgam fillings and found higher Hg levels in the urine of children with amalgam fillings than in children without amalgam fillings. In addition, Pesch et al. (2002) concluded that more reliable estimates of dental amalgam Hg exposure in children may be derived from the number of fillings rather than the surface of amalgam fillings or salvia. Recently, Björnberg et al. (2003) also reported a significant increase in fetal I-Hg exposure, mainly in cord blood, with increasing maternal dental amalgam fillings. Lindow et al. (2003) investigated hair Hg levels in mother–fetal pairs in relation to maternal dental amalgam restorations. These investigators found a positive correlation

between fetal hair Hg level and the number of maternal amalgam fillings.

By implication, the results of the above-referenced dental amalgam studies suggest that the presence of significant concentrations of Hg in the organs of the fetus, neonate, and infant may be a basis for adverse health effects, including the subtle neurodevelopmental disabilities that are associated with Hg exposure. However, there still appears to be little definitive scientific evidence of specific adverse health and neurobehavioral effects in children who have been found to have elevated Hg levels from maternal dental amalgam. The neurobiological and neurodevelopmental effects of maternal dental amalgam Hg exposure in children is an area in need of more extensive scientific investigation.

Effects of mercury exposure on some indigenous, traditional populations

Indigenous children in some parts of the Americas, as well as in some developing nations in other parts of the world, may develop Hg poisoning directly or indirectly through occupational exposure. The use of Hg in gold mining operations has been a major cause of both elemental and methylmercury exposure among indigenous Amer-Indians, especially during the gold rush throughout South American over the past 30 years. The impact of Hg from gold mining operations in the Amazon has been reviewed by Malm (1998). It is estimated that between 2000 and 3000 tons of Hg have been released into the Amazon territory of Brazil alone in the formal and informal mining for gold (Malm, 1998). Other Amazon countries, including Ecuador, Suriname, French Guyana, Guyana, Venezuela, Peru, Bolivia, and Columbia, also have widespread gold mining operations that use Hg in amalgamation. Exposure to Hg^0 results from the burning of Hg amalgam outdoors by miners and indoors by the miners' families, and by shopkeepers to separate gold from alluvial sediment and ore. Malm (1998) reported mercury-in-air level among Amazon gold miners and shopkeepers in excess of the WHO biological limit (50 $\mu g/m^3$) for occupational exposure. Elevated blood Hg levels have been observed in Amer-Indians and Mestizo children living in the gold mining areas of Nambija, Ecuador (Counter, 2003; Counter et al., 1998, 2002). Many of the children who participated in these studies reported exposure to Hg^0 vapors from the burning of a mercury–gold amalgam in the confines of their homes or in the immediate vicinity. The children in these studies, who showed blood Hg levels up to 89 μg/l, may suffer from Hg^0 intoxication from the breathing of Hg vapors and MeHg from the consumption of fish taken from the local rivers where Hg from the gold mining operations is discharge.

Numerous studies have reported high levels of MeHg in the hair of indigenous Amazonian Amer-Indians who live near gold mining operations and who consume local fish contaminated by Hg discharged from the mines (Boischio and Henshel, 1996; Kehrig et al., 1998; Lebel et al., 1996; Leino and Lodenius, 1995; Malm et al., 1995; Grandjean et al., 1999; Santos et al., 2000, 2002). For example, Amazon Basin children living downstream from gold mining operations were found to have above normal hair Hg concentrations in a range that put them at risk for neurodevelopmental disorders (Grandjean et al., 1999). Maurice-Bourgoin et al. (2000) found elevated Hg levels in breast-feeding babies of indigenous Amer-Indian tribes. These investigators concluded that the Hg intoxication found in the infants developed during pregnancy from maternal consumption of fish contaminated by Hg discharged in waterways by local gold mines. Further, Boischio and Henshel (2000) found elevated Hg levels in the breast milk of breast-feeding mothers and the hair of their infants. The concentration of Hg in breast milk is similar to that of blood and represents recent exposure. The concentration of Hg in hair, on the other hand, reflects long-term Hg exposure.

Elevated Hg levels in infants and children have been reported for other indigenous cultures, including Inuits in Greenland (Bjerregaard and Hansen, 2000; Hansen et al., 1990, 1991) and Northern Québec (Muckle et al., 2001), women of childbearing age among the James Bay Quebec Cree (Girard et al., 1996) and Ojibwa American Indians (Gerstenberger et al., 1997). Similarly, a recent report by Akagi et al. (2000) showed elevated Hg levels in school children residing near gold mining operations in the Philippines. In summary, there is considerable evidence that the children of indigenous communities in many nations are exposed to Hg from gold mining operations and industrial discharge, and suffer adverse heath effects. Further study should be conducted to examine the extent and the neurodevelopmental consequences of Hg exposure in indigenous children who live in gold mining communities and other occupational settings where Hg is used. Further, remediation efforts should be initiated to protect indigenous populations from exposure to industrial Hg.

Discussion

The health hazards of Hg exposure in children and adults have been known for centuries. However, the sentinel events in modern times that raised public awareness of the serious consequences of Hg exposure were the Minamata, Japan, and Iraqi disasters. Both of these Hg poisoning epidemics revealed severe neurological damage that results from exposure to high doses of Hg, specifically MeHg. Based on interpretation of data from the Iraqi incident, the WHO (1990) concluded that an increased risk (5%) of adverse neurodevelopmental outcomes may occur when maternal hair Hg levels exceed about 10–20 ppm, and a high risk (greater than 30%) is present when maternal hair Hg concentrations exceed 70 ppm (WHO, 1990). The "safe" level in cord blood is considered to be 29 ppb (Pichichero et al., 2002). However, a threshold at which there are no apparent developmental effects of MeHg has

not been established. Some studies have shown adverse effects even below 10 ppm. A reference dose (RfD) for ingested MeHg has been set by the U.S. Environmental Protection Agency (EPA) for human exposure. An RfD refers to the amount of MeHg that can be ingested over a lifetime without producing adverse health outcomes. The EPA's RfD for ingested MeHg is 0.1 μg/kg/day (μg/kg bw/day or microgram per kilogram of body weight per day). It has been suggested that a food preparation factor be used in risk assessment, because when fish is cooked (especially by deep-frying), the concentration of Hg in μg/kg increases, although the cooked fish retains the same amount or mass of Hg as raw fish (Burger et al., 2003; Morgan et al., 1997). The ATSDR uses a different minimal risk level (i.e., safe level) of 0.3 μg/kg/day, which is based on the Seychelles Islands study. The National Academy of Sciences (NRC, 2000) concluded that the EPA's RfD was scientifically justified, but that the Faroe Islands study should be used as the critical study, instead of the Iraqi data as had been previously used by the EPA. Some reports (Budtz-Jorgensen et al., 2000; EPA, 1997) have attempted to calculate benchmarks for threshold effect levels resulting in adverse neurobehavioral effects. Based on one endpoint (the Boston Naming Test) of the Faroe Islands study, the National Academy of Sciences (NRC, 2000) recommended a benchmark dose level of 58 μg/l of Hg in cord blood. This specific benchmark dose refers to the lower 95% confidence limit of Hg in cord blood that is estimated to produce a 5% increase in the incidence of abnormal scores on the Boston Naming Test. It was also recommended that the benchmark dose be multiplied by an uncertainty factor of 10 to yield an RfD of 5.8 μg/l in cord blood (NRC, 2000).

Forty-one states in the United States have advisories on limiting fish intake, especially for pregnant women and women who may become pregnant (Mahaffey, 1998). The FDA has advised pregnant women and women expecting to become pregnant to avoid eating the long-lived, larger fish that feed on other fish, such as tilefish, king mackerel, swordfish, and shark. These fish species have high MeHg concentrations in their tissues (see Tables 5 and 6). The FDA further indicated that it is safe for women to consume 12 oz of other fish in 1 week. A limit or "action level" of 1 ppm has been set by the FDA for Hg levels in fish and treated seed grain. That is, commercial fish or seed grain with this level of Hg cannot be sold to the public (ATSDR, 1999; Goldman and Shannon, 2001).

Table 5
Mean and range of mercury (Hg) levels in seafood species with the highest Hg levels

Species	Mean (ppm)	Range (ppm)	No. of samples
Tilefish	1.45	0.65–3.73	60
Swordfish	1.00	0.10–3.22	598
King mackerel	0.73	0.30–1.67	213
Shark	0.96	0.05–4.54	324

Data from U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Seafood (May 2001).

Table 6
Mean and range of mercury (Hg) levels in seafood species with lower Hg levels

Species	Mean (ppm)	Range (ppm)	No. of samples
Grouper (*Mycteroperca*)	0.43	0.05–1.35	64
Tuna (fresh or frozen)	0.32	ND–1.30	191
Lobster Northern (American)	0.31	0.05–1.31	88
Grouper (*Epinephelus*)	0.27	0.19–0.33	48
Halibut	0.23	0.02–0.63	29
Sablefish	0.22	ND–0.70	102
Pollock	0.20	ND–0.78	107
Tuna (canned)	0.17	ND–0.75	248
Crab Blue	0.17	0.02–0.50	94
Crab Dungeness	0.18	0.02–0.48	50
Crab Tanner	0.15	ND–0.38	55
Crab King	0.09	0.02–0.24	29
Scallop	0.05	ND–0.22	66
Catfish	0.07	ND–0.31	22
Salmon (fresh, frozen, or canned)	ND	ND–0.18	52
Oysters	ND	ND–0.25	33
Shrimps	ND	ND	22

Data from U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Seafood (May 2001).

The Seychelles study (Davidson et al., 1995, 1998) has been criticized by some investigators involved in the Faroe Islands project as being uninformative (Grandjean and White, 1999). Grandjean and White (1999) stated that cord-blood mercury concentration is a better predictor of neurodevelopmental effects than maternal hair Hg, which was used in the SCDS. Grandjean and White (1999) also stated that the test battery used by Davidson et al. (1998) did not fully meet the criteria set forth at a symposium concerned with environmental pollution and health effects (White et al., 1998). They further stated that: (1) test sensitivity was insufficient because American tests were translated into Creole and administered in another culture by nurses, (2) adjusting the tests to American norms was problematic, and (3) bilingualism may have affected the verbal test data. It may well be that bilingualism will have a bearing on verbal test results, but it would be expected that the children would perform more poorly because of multilingual influences. Stern and Gochfeld (1999) also attacked the SCDS for it choice of biomarker (Hg in maternal hair), stating that cord blood was a better predictor of subtle neurodevelopmental impairment. Mahaffey (1998) suggested that interpretations of the data from the SCDS (Davidson et al., 1998) was difficult because at the age of 66 months, several neurodevelopmental endpoints indicated better scores for children in the highest exposure groups. She also complained about the "robust" developmental status of the Seychelles children as shown in an earlier SCDS report (Davidson et al., 1995), probably referring to the finding that the Seychellois infants were 2 SD above U.S. norms at 19 and 29 months on the Bayley Scales of Infant Development. Davidson et al. (1995) inferred that

this finding was consistent with previous studies suggesting motoric precocity in African children (Allen and Alexander, 1990). There is, however, no unequivocal evidence for motoric precocity in African or African-American children. Mahaffey (1998) felt that some of the tests used in the SCDS were not sensitive enough to detect subtle neurodevelopmental problems. The Seychelles group thought that some of the criticism was not scientifically based (Davidson et al., 1999).

In summary, the two major longitudinal epidemiological studies of Hg exposure in children continue to show divergent results. The Seychelles study has followed its mother–child pairs from 6 months to 9 years of age and found no adverse developmental effects, even when using a large array of neurodevelopmental endpoints that should be sensitive to MeHg exposure. The Faroe Islands study on the other hand continues to show neurodevelopmental effects in the domains of language, attention and memory, and less so in visual–spatial abilities. In the Faroe Islands cohort, subtle effects were shown, indicating that at the age of 7 years, a -1 to 2-month cognitive delay occurred for each doubling of prenatal mercury exposure. Although many of these effects may be within test variability and may not be of clinical or biological significance, Grandjean (1999) and Grandjean et al. (1997) have evoked the argument presented in the lead (Pb) literature that small deviations from average may have a significant bearing on the normal population distribution in which more children will be on the low end and fewer children on the high end of the distribution (Needleman et al., 1982; Stein et al., 2002). The U.S. Environmental Protection Agency has probably taken the most reasoned approach in using the Faroe Island study as the critical study for the protection of public health.

There are possibly numerous factors contributing to the divergent results of these two methodologically sound investigations, some of which are probably unknown at this time. The developmental endpoints used no longer seem to be a viable explanation for the different results from the two studies because the SCDS in its recent evaluation of the Seychellois children at 9 years of age used an extensive array of domain-specific and global neurodevelopmental tests that were similar to those used by the Faroe group (Myers et al., 2003). The use of different biomarkers (cord blood vs. maternal hair Hg concentration) by the two studies to ascertain prenatal exposure may have some bearing on the statistical results. Agreement on the most appropriate indicator media for ascertaining developmental effects related to MeHg exposure is lacking, and further scientific study is necessary to reach a conclusion. The choice of covariates for the statistical models may also be an issue that needs scrutinizing. Perhaps one of the more important differences between the two studies is the study population. Inhabitants of the Seychelles Island eat fish with lower MeHg concentrations, whereas the Faroese consume whale meat (which is high in MeHg) and blubber, which is contaminated by PCBs and other pollutants. Further research is needed to sort out the potential interaction of PCBs and MeHg exposure on neurodevelopmental outcomes.

It has been postulated that thimerosal-containing vaccines induce developmental disorders, such as autism, but large population-based studies show no definitive evidence for this. However, because of potential subtle neurodevelopmental effects, the United States has mandated the phasing-out of thimerosal-containing vaccines. Other countries, such as Sweden and Denmark, eliminated thimerosal in vaccines more than 10 years ago. However, thimerosal may still be found in vaccines used in some developing countries.

Elemental Hg exposure through accidents, magico-religious rituals, and vapors from amalgam burning in gold mining operations continues to be a public health concern. The cessation of the manufacture of Hg-containing thermometers, and other such devices will reduce the potential for Hg exposure through accidents and in the workplace. Further, education of indigenous populations about the hazards of Hg use in gold mining operations, and the introduction of public health information to religious groups that use Hg^0 in their ritualistic practices may assist in reduction of pediatric Hg exposure in these groups.

Inorganic Hg remains an important source of Hg intoxication, primarily through the use of skin-lightening creams and teething powders, which may produce neurological, nephrological, and dermatological disorders. Although the manufacturing of some Hg-containing creams is illegal in America and some European nations, the use of Hg-based skin-lightening cosmetics has increased worldwide and has caused widespread Hg-induced health effects in some countries. Because it has been shown that the I-Hg in some cosmetics may cross the placenta to reach the fetus, pregnant women and women of childbearing age should avoid the use of Hg-based cosmetics.

The health effects of Hg amalgam fillings (generally consisting of 50% Hg), which produce a combination of Hg^0 vapor in the oral cavity and I-Hg in the blood and body tissues, have been a subject of concern for years. Some scientific studies suggest that Hg from maternal dental amalgam fillings may influence prenatal and postnatal development because of the high concentrations of Hg observed in fetal tissue and neonatal blood. Numerous studies have shown that as the number of maternal amalgam fillings increase, the amount of Hg in the tissues of the fetus increases. This suggests potentially harmful consequences to the developing nervous system, which is highly vulnerable to neurotoxic metals such as Hg and Pb. However, there appears to be little scientific information on the neurodevelopmental effects in children born to mothers with Hg amalgam fillings. This is an area in which population-based research is needed.

In summary, this review presented and overview of the sources and effects of Hg exposure in children. It covered the most recent and ongoing large cohort longitudinal studies of MeHg intoxication in children, as well as con-

temporary studies of MeHg exposure in pregnant women who consumed varying amounts of fish, the primary source of MeHg intoxication. Accidental, occupational, and ritualistic exposure to Hg^0 vapor in both modern and traditional societies was explored. Lastly, the toxic effects of I-Hg from the use of Hg-based topical cosmetics and teething powders, as well as from dental amalgams were examined.

References

Abraham, J.E., Svare, C.W., Frank, C.W., 1984. The effect of dental amalgam restorations on blood mercury levels. J. Dent. Res. 63, 71–73.

Adebajo, S.B., 2002. An epidemiological survey of the use of cosmetic skin lightening cosmetics among traders in Lagos, Nigeria. West Afr. Med. J. 21, 51–55.

Agency for Toxic Substances and Disease Registry (ATSDR), 1992. U.S. Dept. Public Health, Atlanta, GA.

Agency for Toxic Substances and Disease Registry (ATSDR), 1999. U.S. Dept. Public Health, Atlanta, GA.

Akagi, H., Castillo, E.S., Cortes-Maramba, N., Francisco-Rivera, A.T., Timbang, T.D., 2000. Health assessment for mercury exposure among schoolchildren residing near a gold processing and refining plant in Apokon, Tagum, Davao del Norte, Philippines. Sci. Total Environ. 259, 31–43.

Albers, J.W., Cavender, G.D., Levine, S.P., Langolf, G.D., 1982. Asymptomatic sensorimotor polyneuropathy in workers exposed to elemental mercury. Neurology 32, 1168–1174.

Albrecht, J., Matyja, E., 1996. Glutamate: a potential mediator of inorganic mercury neurotoxicity. Metab. Brain Dis. 11, 175–184.

Allen, M.C., Alexander, G.R., 1990. Gross motor milestones in preterm infants: correction for degree of prematurity. J. Pediatr. 116, 955–959.

Al-Saleh, I., Al-Doush, I., 1997. Mercury content in skin-lightening creams and potential hazards to the health of Saudi women. J. Toxicol. Environ. Health 51, 123–130.

Al-Saleh, I., Shinwari, N., 1997. Urinary mercury levels in females: influence of skin-lightening creams and dental amalgam fillings. BioMetals 10, 315–323.

American Academy of Pediatrics, 1999. Committee on Infectious Diseases and Committee on Environmental Health, Thimerosal in vaccines: an interim report to clinicians. Pediatrics 104, 570–574.

American Family Physician, 1992. Mercury toxicity. Agency for toxic substance and disease registry. Am. Fam. Physician 46, 1731–1741.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Amin-Zaki, L., Elhassani, S., Majeed, M.A., Clarkson, T.W., Doherty, R.A., Greenwood, M., 1974. Intra-uterine methylmercury poisoning in Iraq. Pediatrics 54, 587–595.

Ask, K., Åkesson, A., Berglund, M., Vahter, M., 2002. Inorganic mercury and methylmercury in placentas of Swedish women. Environ. Health Perspect. 110, 523–526.

Bakir, F., Damluji, S.F., Amin-Zaki, L., Murtadha, M., Khalidi, A., Al Rawi, N.Y., Tikriti, S., Dhahir, H.I., Clarkson, T.W., Smith, J.C., Doherty, R.A., 1973. Methylmercury poisoning in Iraq. Science 181, 230–241.

Ball, L.K., Ball, R., Pratt, R.D., 2001. An assessment of thimerosal use in childhood vaccines. Pediatrics 107, 1147–1154.

Baskin, D.S., Ngo, H., Didenko, V.V., 2003. Thimerosal induces DNA breaks, caspase-3 activation, membrane damage, and cell death in cultured human neurons and fibroblasts. Toxicol. Sci. 74, 361–368.

Bernard, S., Enayati, A., Redwood, L., Roger, H., Binstock, T., 2001. Autism: a novel form of mercury poisoning. Med. Hypotheses 56, 462–471.

Bjerregaard, P., Hansen, J.C., 2000. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. Sci. Total Environ. 245, 195–202.

Björnberg, K.A., Vahter, M., Petersson-Grawe, K., Glynn, A., Cnattingius, S., Darnerud, P.O., Atuma, S., Aune, M., Becker, W., Berglund, M., 2003. Methyl mercury and inorganic mercury in Swedish pregnant women and in cord blood: influence of fish consumption. Environ. Health Perspect. 111, 637–641.

Boischio, A.P., Henshel, D.S., 1996. Risk assessment of mercury exposure through fish consumption by the riverside people in the Madeira basin, Amazon, 1991. Neurotoxicology 17, 169–175.

Boischio, A.P., Henshel, D.S., 2000. Linear regression models of methyl mercury exposure during prenatal and early postnatal life among riverside people along the upper Madeira river, Amazon. Environ. Res. 83, 150–161.

Braun, M.M., Mootrey, G.T., Salive, M.E., Chen, R.T., Ellenberg, S.S., 2000. Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS). Pediatrics 106, E51.

Brookes, N., 1992. In vitro evidence for the role of glutamate in the CNS toxicity of mercury. Toxicology 76, 245–256.

Budtz-Jorgensen, E., Grandjean, P., Keiding, N., White, R.F., Weihe, P., 2000. Benchmark dose calculations of methylmercury-associated neurobehavioral deficits. Toxicol. Lett. 112–113, 193–199.

Burger, J., Dixon, C., Boring, C.S., Gochfeld, M., 2003. Effect of deep-frying fish on risk from mercury. J. Toxicol. Environ. Health, Part A 66, 817–828.

Campbell, J.S., 1948. Acute mercurial poisoning by inhalation of metallic vapour in an infant. Can. J. Med. 58, 72–75.

Castoldi, A.F., Coccini, T., Ceccatelli, S., Manzo, L., 2001. Neurotoxicity and molecular effects of methylmercury. Brain Res. Bull. 55, 197–203.

Centers for Disease Control and Prevention (CDC), 1991. Current trends acute and chronic poisoning from residential exposures to elemental mercury—Michigan, 1989–1990. Morb. Mort. Wkly. Rep. 40, 393–395.

Centers for Disease Control and Prevention (CDC), 1996a. Mercury poisoning associate with beauty cream—Arizona, California, New Mexico and Texas. Morb. Mort. Wkly. Rep. 45, 400–403.

Centers for Disease Control and Prevention (CDC), 1996b. Update: mercury poisoning associate with beauty cream—Arizona, California, New Mexico and Texas. Morb. Mort. Wkly. Rep. 45, 633–635.

Centers for Disease Control and Prevention (CDC), 2001. Blood and hair mercury levels in young children and women of childbearing age—United States, 1999. Morb. Mort. Wkly. Rep. 50, 140–143.

Chang, L.W., 1977. Neurotoxic effects of mercury: a review. Environ. Res. 14, 329–373.

Cherry, D., Lowry, L., Velez, L., Cotrell, C., Keyes, D.C., 2002. Elemental mercury poisoning in a family of seven. Fam. Commun. Health 24, 1–8.

Clarkson, T.W., 1993. Mercury: major issues in environmental health. Environ. Health Perspect. 100, 31–38.

Clarkson, T.W., 2002. The three modern faces of mercury. Environ. Health Perspect. 110, 11–23.

Cordier, S., Grasmick, C., Paquier-Passelaigue, M., Mandereau, L., Weber, J.P., Jouan, M., 1998. Mercury exposure in French Guiana: levels and determinants. Arch. Environ. Health 53, 299–303.

Cordier, S., Garel, M., Mandereau, L., Morcel, H., Doineau, P., Gosme-Seguret, S., Josse, D., White, R., Amiel-Tison, C., 2002. Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. Environ. Res. 89, 1–11.

Counter, S.A., 2003. Neurophysiological anomalies in brainstem responses of mercury-exposed children of Andean gold miners. J. Occup. Environ. Med. 45, 87–95.

Counter, S.A., Buchanan, L.H., Laurell, G., Ortega, F., 1998. Blood mercury and auditory neuro-sensory responses in children and adults in the Nambija gold mining area of Ecuador. Neurotoxicology 19, 185–196.

Counter, S.A., Buchanan, L.H., Ortega, F., Laurell, G., 2002. Elevated blood mercury and neuro-otological observations in children of the Ecuadorian gold mines. J. Toxicol. Environ. Health, Part A 65, 149–163.

Cranmer, M., Gilbert, S., Cranmer, J., 1996. Neurotoxicity of mercury—

Indicators and effects of low-level exposure: overview. Neurotoxicology 17, 9–14.
Davidson, P.W., Myers, G.J., Cox, C., Shamlaye, C., Marsh, D.O., Tanner, M.A., Berlin, M., Sloane-Reeves, J., Cernichiari, E., Choisy, O., Choi, A., Clarkson, T.W., 1995. Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months. Neurotoxicology 16, 677–688.
Davidson, P.W., Myers, G.J., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., Cernichiari, E., Needham, L., Choi, A., Wang, Y., Berlin, M., Clarkson, T.W., 1998. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. J. Am. Med. Assoc. 280, 701–707.
Davidson, P.W., Myers, G.J., Cox, C., Cernichiari, E., Clarkson, T.W., Shamlaye, C., 1999. Effects of methylmercury exposure on neurodevelopment. J. Am. Med. Assoc. 281, 897.
Davidson, P.W., Palumbo, D., Myers, G.J., Cox, C., Shamlaye, C.F., Sloane-Reeves, J., Cernichiari, E., Wilding, G.E., Clarkson, T.W., 2000. Neurodevelopmental outcomes of Seychellois children from the pilot cohort a 108 months following prenatal exposure to methylmercury from a maternal fish diet. Environ. Res., Sec. A 84, 1–11.
del Giudice, P., Yves, P., 2002. The widespread use of skin lightening creams in Senegal: a persistent public health problem in West Africa. Int. J. Dermatol. 41, 69–72.
Denny, M.F., Atchison, W.D., 1996. Mercurial-induced alterations in neuronal divalent cation homeostasis. Neurotoxicology 17, 47–62.
Drasch, G., Schupp, I., Höfl, H., Reinke, R., Roider, G., 1994. Mercury burden of human fetal and infant tissues. Eur. J. Pediatr. 153, 607–610.
Dyall-Smith, D.J., Scurry, J.P., 1990. Mercury pigmentation and high mercury levels from the use of a cosmetic cream. Med. J. Aust. 153, 409–410, 414–415.
Environmental Protection Agency, 1997. Mercury Study Report to Congress. US Environment Protection Agency, Washington, DC.
Evens, C.C., Martin, M.D., Woods, J.S., Soares, H.L., Bernardo, M., Leitao, J., Simmonds, P.L., Liang, L., DeRouen, T.J., 2001. Examination of dietary methylmercury exposure in the Casa Pia Study of the health effects of dental amalgams in children. Toxicol. Environ. Health, Part A 64, 521–530.
Florentine, M.J., Sanfilippo, D.J., 1991. Elemental mercury poisoning. Clin. Pharmacol. 10, 213–221.
Forman, J., Moline, J., Cernichiari, E., Sayegh, S., Torres, J.C., Landrigan, M.M., Hudson, J., Adel, H.N., Landrigan, P.J., 2000. A cluster of pediatric metallic mercury exposure cases treated with meso-2,3-dimercaptosuccinic acid (DMSA). Environ. Health Perspect. 108, 575–577.
Garza-Ocanas, L., Torres-Alanis, O., Pineyro-Lopez, A., 1997. Urinary mercury in twelve cases of cutaneous mercurous chloride (calomel) exposure: effect of sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) therapy. J. Toxicol., Clin. Toxicol. 35, 653–655.
Geier, M.R., Geier, D.A., 2003. Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. Exp. Biol. Med. 228, 660–664.
Gerstenberger, S.L., Tavris, D.R., Hansen, L.K., Pratt-Shelley, J., Dellinger, J.A., 1997. Concentrations of blood and hair mercury and serum PCBs in an Ojibwa population that consumes Great Lakes region fish. J. Toxicol., Clin. Toxicol. 35, 377–386.
Girard, M., Noel, F., Dumont, C., 1996. Varying mercury exposure with varying food source in a James Bay Cree community. Arctic Med. Res. 55, 69–74.
Goldman, L.R., Shannon, M.W., 2001. Technical report: mercury in the environment: implications for pediatricians. Pediatrics 108, 197–205.
Goldwater, L.J., 1957. The toxicology of inorganic mercury. Ann. N. Y. Acad. Sci. 65, 498–503.
Gopal, K.V., 2003. Neurotoxic effects of mercury on auditory cortex networks growing on microelectrode arrays: a preliminary analysis. Neurotoxicol. Teratol. 25, 69–76.
Grandjean, P., 1999. Mercury risks: controversy or just uncertainty? Public Health Rep. 114, 512–515.
Grandjean, P., White, R.F., 1999. Effects of methylmercury exposure on neurodevelopment. J. Am. Med. Assoc. 281, 896.
Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sørensen, N., Dahl, R., Jørgensen, P.J., 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19, 417–428.
Grandjean, P., Weihe, P., White, R.F., Debes, F., 1998. Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. Environ. Res., Sect. A 77, 165–172.
Grandjean, P., White, R.F., Nielsen, A., Cleary, D., de Oliveira Santos, E.C., 1999. Methylmercury neurotoxicity in Amazonian children downstream from gold mining. Environ. Health Perspect. 107, 587–591.
Halbach, S., Clarkson, T.W., 1978. Enzymatic oxidation of mercury vapor by erythrocytes. Biochim. Biophys. Acta 523, 522–531.
Halsey, N.A., 1999. Limiting infant exposure to thimerosal in vaccines and other sources of mercury. J. Am. Med. Assoc. 282, 1763–1766.
Hansen, J.C., Tarp, U., Bohm, J., 1990. Prenatal exposure to methyl mercury among Greenlandic polar Inuits. Arch. Environ. Health 45, 355–358.
Hansen, J.C., Jensen, T.G., Tarp, U., 1991. Changes in blood mercury and lead levels in pregnant women in Greenland 1983–1988. Arctic Med. Res., 605–607 (Suppl.).
Hirayama, K., 1985. Effects of combined administration of thiol compounds and methylmercury chloride on mercury distribution in rats. Biochem. Pharmacol. 37, 2030–2032.
Houeto, P., Sandouk, P., Baud, F.J., Levillain, P., 1994. Elemental mercury vapour toxicity: treatment and levels in plasma and urine. Hum. Exp. Toxicol. 13, 848–852.
Hudson, P.J., Vogt, R.L., Brondum, J., Witherell, L., Myers, G., Paschal, D.C., 1987. Elemental mercury exposure among children of thermometer plant workers. Pediatrics 79, 935–938.
Hviid, A., Stellfeld, M., Wohlfahrt, J., Melbye, M., 2003. Association between thimerosal-containing vaccine and autism. J. Am. Med. Assoc. 290, 1763–1766.
Isselbacher, K.J., Braunwald, E., Wilson, J.D., Martin, J.B., Fauci, A.S., Kasper, D.L. (Eds.), 1994. Harrison Principles of Internal Medicine, 13th ed. McGraw-Hill, New York.
Jacobson, J.L., Jacobson, S.W., 1997. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N. Engl. J. Med. 336, 660–661.
Jensen, S., Jernelov, A., 1969. Biological methylation of mercury in aquatic organisms. Nature 223, 753–754.
Jovanovic, S., Maisner, V., Horras-Hun, G., Gabrio, T., Schwenk, M., 1997. Poisoning of a family by a mercury-containing ointment. Gesundheitswesen 59, 405–408.
Kehrig, H.A., Malm, O., Akagi, H., Guimaraes, J.R., Torres, J.P., 1998. Methylmercury in fish and hair samples from the Balbina Feservior, Brazilian Amazon. Environ. Res. 77, 84–90.
Kerper, L.E., Ballatori, N., Clarkson, T.W., 1992. Methylmercury transport across the blood–brain barrier by an amino acid carrier. Am. J. Physiol. 262, R761–R765.
Kimmel, S.R., 2002. Vaccine adverse events: separating myth from reality. Am. Fam. Physician 66, 2113–2120.
Kjellström, T., Kennedy, P., Wallis, S., Mantell, C., 1986. Physical and mental development of children with prenatal exposure to mercury from fish: stage 1. Preliminary tests at age 4. Natl. Swed. Environ. Board Rep., vol. 3642. Solna, Sweden.
Kjellström, T., Kennedy, P., Wallis, S., Stewart, A., Friberg, L., Lind, B., Wutherspoon, T., Mantell, C., 1989. Physical and mental development of children with prenatal exposure to mercury from fish: stage 2. Interviews and psychological tests at age 6. Natl. Swed. Environ. Board Rep., vol. 3642. Solna, Sweden.
Koos, B.J., Longo, L.D., 1976. Mercury toxicity in the pregnant woman, fetus, and newborn infant. A review. Am. J. Obstet. Gynecol. 26, 390–409.
Lauwerys, R., Bonnier, C., Evrard, P., Gennart, J.P., Bernard, A., 1987. Prenatal and early postnatal intoxication by inorganic mercury resulting

from the maternal use of mercury containing soap. Hum. Toxicol. 6, 253–256.
Lebel, J., Mergler, D., Lucotte, M., Amorim, M., Dolbec, J., Miranda, D., Arantès, G., Rheault, I., Pichet, P., 1996. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury. Neurotoxicology 17, 157–168.
Leino, T., Lodenius, M., 1995. Human hair mercury levels in Tucurui area, State of Para, Brazil. Sci. Total Environ. 175, 119–125.
Leong, C.C., Syed, N.I., Lorscheider, F.L., 2001. Retrograde degeneration of neurite membrane structural integrity of nerve growth cones following in vitro exposure to mercury. NeuroReport 12, 733–737.
Liang, G., Järlebark, L., Ulfendahl, M., Moore, E.J., 2003. Mercury (Hg^{2+}) suppression of potassium currents of outer hair cells. Neurotoxicol. Teratol. 25, 349–359.
Lien, D.C., Todoruk, D.N., Rajani, H.R., Cook, D.A., Herbert, F.A., 1983. Accidental inhalation of mercury vapour: respiratory and toxicologic consequences. Can. Med. Assoc. J. 129, 591–595.
Lindow, S.W., Knight, R., Batty, J., Haswell, S.J., 2003. Maternal and neonatal hair mercury concentrations: the effect of dental amalgam. Br. J. Obstet. Gynaecol. 110, 287–291.
Madsen, K.M., Lauritsen, M.B., Pedersen, C.B., Thorsen, P., Plesner, A.M., Andersen, P.H., Mortensen, P.B., 2003. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics 112, 604–606.
Magos, L., 2001. Review on the toxicity of ethyl mercury including its presence as a preservative in biological and pharmaceutical preparations. J. Appl. Toxicol. 21, 1–5.
Magos, L., 2003. Neurotoxic character of thimerosal and the allometric extrapolation of adult clearance half-time to infants. J. Appl. Toxicol. 23, 263–269.
Mahaffey, K.R., 1998. Methylmercury exposure and neurotoxicity. J. Am. Med. Assoc. 280, 737–738.
Malm, O., 1998. Gold mining as a source of mercury exposure in the Brazilian Amazon. Environ. Res. 77, 73–78.
Malm, O., Branches, F.J., Akagi, H., Castro, M.B., Pfeiffer, W.C., Harada, M., Bastos, W.R., Kato, H., 1995. Mercury and methylmercury in fish and human hair from the Tapajos river basin, Brazil. Sci. Total Environ. 11, 141–150.
Marsh, D.O., Turner, M.D., Smith, J.C., Allen, P., Richdale, N., 1995. Fetal methylmercury study in a Peruvian fish-eating population. Neurotoxicology 16, 717–726.
Matthes, F.T., Kirschner, R., Yow, M.D., Brennan, J.C., 1958. Acute poisoning associated with inhalation of mercury vapor: report of four cases. Pediatrics 22, 675–688.
Maurice-Bourgoin, L., Quiroga, I., Chincheros, J., Courau, P., 2000. Mercury distribution in waters and fishes of the upper Madeira rivers and mercury exposure in riparian Amazonian populations. Sci. Total Environ. 260, 73–86.
McKeown-Eyssen, G.E., Ruedy, J., Neims, A., 1983. Methyl mercury exposure in northern Quebec: II. Neurologic findings in children. Am. J. Epidemiol. 118, 470–479.
McRill, C., Boyer, L.V., Flood, T.J., Ortega, L., 2000. Mercury toxicity due to use of a cosmetic cream. J. Occup. Environ. Med. 42, 4–7.
Miller, A.L., 1998. Dimercaptosuccinic acid (DMSA), a non-toxic, water-soluble treatment for heavy metal toxicity. Altern. Med. Rev. 3, 199–207.
Moller-Madsen, B., 1992. Localization of mercury in CNS of rat: V. Inhalation exposure to metallic mercury. Arch. Toxicol. 66, 79–89.
Morgan, J., Berry, M.R., Graves, R.L., 1997. Effects of commonly used cooking practices on total mercury concentration in fish and their impact on exposure assessments. J. Exposure Anal. Environ. Epidemiol. 7, 119–134.
Moutinho, M.E., Tompkins, A.L., Roland, T.W., Banson, B.B., Jackson, A.H., 1981. Acute mercury vapor poisoning: fatality in an infant case. Am. J. Dis. Child. 135, 42–44.
Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W., Jacobson, J.L., 2001. Prenatal exposure of the northern Québec Inuit infants to environmental contaminants. Environ. Health Perspect. 109, 1291–1299.
Murata, K., Weihe, P., Renzoni, A., Debes, F., Vasconcelos, R., Zino, F., Araki, S., Jørgensen, P.J., White, R.F., Grandjean, P., 1999a. Delayed evoked potentials in children exposed to methylmercury from seafood. Neurotoxicol. Teratol. 19, 417–428.
Murata, K., Weihe, P., Araki, S., Budtz-Jørgensen, E., Grandjean, P., 1999b. Evoked potentials in Faroese children prenatally exposed to methylmercury. Neurotoxicol. Teratol. 21, 471–472.
Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Tanner, M.A., Choisy, O., Sloane-Reeves, J., Marsh, D.O., Cernichiari, E., Choi, A., Berlin, M., Clarkson, T.W., 1995a. Pilot neurodevelopment study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet. Neurotoxicology 16, 629–638.
Myers, G.J., Marsh, D.O., Davidson, P.W., Cox, C., Shamlaye, C.F., Tanner, M.A., Choi, A., Cernichiari, E., Choisy, O., Clarkson, T.W., 1995b. Main neurodevelopment study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months. Neurotoxicology 16, 653–664.
Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C., Cernichiari, E., Clarkson, T.W., 2000. Twenty-seven years studying the human neurotoxicity of methylmercury exposure. Environ. Res., Sect. A 83, 275–285.
Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Palumbo, D., Cernichiari, E., Sloane-Reeves, J., Wilding, G.E., Kost, J., Huang, L.S., Clarkson, T.W., 2003. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 361, 1686–1692.
Nadarajah, V., Neiders, M.E., Aguirre, A., Cohen, R.E., 1996. Localized cellular inflammatory responses to subcutaneously implanted dental mercury. J. Toxicol. Environ. Health 49, 113–125.
National Research Council, Committee on the Toxicological Effects of Methylmercury, 2000. Toxicological Effects of Methylmercury. National Academy Press, Washington, DC.
Needleman, H.L., Leviton, A., Bellinger, D., 1982. Lead-associated intellectual deficit. N. Engl. J. Med. 306, 367.
Nelson, K.B., Bauman, M.L., 2003. Thimerosal and autism. Pediatrics 111, 674–679.
Newland, M.C., Warfvinge, K., Berlin, M., 1996. Behavioral consequences of in utero exposure to mercury vapor: alterations in lever-press durations and learning in squirrel monkeys. Toxicol. Appl. Pharmacol. 139, 374–386.
Oskarsson, A., Schütz, A., Skerfving, S., Hallén, I.P., Ohlin, B., Lagerkvist, B.J., 1996. Total and inorganic mercury in breast milk and blood in relation to fish consumption and amalgam filling sin lactating women. Arch. Environ. Health 51, 234–241.
Otto, M., Ahlemeyer, C., Tasche, H., von Mehlendahl, K.E., 1994. Endemic mercury burden caused by a bleaching ointment in Balkan refugees. Gesundheitswesen 56, 686–689.
Ozuah, P.O., Lesser, M.S., Woods, J.S., Choi, H., Markowitz, M., 2003. Mercury exposure in an urban pediatric population. Ambul. Pediatr. 3, 24–26.
Palmer, R.B., Godwin, D.A., McKinney, P.E., 2000. Transdermal kinetics of a mercurous chloride beauty cream: an in vitro human skin analysis. J. Toxicol., Clin. Toxicol. 38, 701–707.
Pamphlett, R., Kum-Jew, S., 2001. Mercury vapor uptake into the nervous system of developing mice. Neurotoxicol. Teratol. 23, 191–196.
Parran, D.K., Barone Jr., S., Mundy, W.R., 2003. Methylmercury decreases NGF-induced TrkA autophosphorylation and neurite outgrowth in PC12 cells. Brain Res. Dev. Brain Res. 141, 71–81.
Pesch, A., Wilhelm, M., Rostek, U., Schmitz, N., Weishoff-Houben, M., Ranft, U., Idel, H., 2002. Mercury concentrations in urine, scalp hair, and saliva in children from Germany. J. Exposure Anal. Environ. Epidemiol. 12, 252–258.
Pichichero, M.E., Cernichiari, E., Lopreiato, J., Treanor, J., 2002. Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study. Lancet 360, 1737–1741.
Ramirez, G.B., Cruz, M.C.V., Pagulayan, O., Ostrea, E., Dalisay, C., 2000.

The Tagum study I: analysis and clinical correlates of mercury in maternal and cord blood, breast milk, meconium, and infant's hair. Pediatrics 106, 774–781.
Ratcliffe, H.E., Swanson, G.M., Fischer, L.J., 1996. Human exposure to mercury: a critical assessment of the evidence of adverse health effects. J. Toxicol. Environ. Health 49, 221–270.
Reuhl, K.R., Chang, L.W., 1979. Effects of methylmercury on the development of the nervous system: a review. Neurotoxicology 1, 21–55.
Rice, D.C., Gilbert, S.G., 1992. Exposure to methyl mercury from birth to adulthood impairs high-frequency hearing in monkeys. Toxicol. Appl. Pharmacol. 115, 6–10.
Riley, D.M., Newby, C.A., Leal-Almeraz, T.O., Thomas, V.M., 2001. Assessing elemental mercury vapor exposure from cultural and religious practices. Environ. Health Perspect. 109, 779–784.
Rogan, W.J., Gladen, B.C., 1991. PCBs, DDE, and child development at 18 and 24 months. Ann. Epidemiol. 1, 407–413.
Rogan, W.J., Gladen, B.C., 1992. Neurotoxicology of PCBs and related compounds. Neurotoxicology 13, 27–35.
Rogan, W.J., Gladen, B.C., McKinney, J.D., Carreras, N., Hardy, P., Thullen, J., Tinglestad, J., Tully, M., 1986. Neonatal effects of transplacental exposure to PCBs and DDE. J. Pediatr. 109, 335–341.
Sager, P.R., Doherty, R.A., Rodier, P.M., 1982. Effects of methylmercury on developing mouse cerebellar cortex. Exp. Neurol. 77, 179–193.
Samuels, E.R., Heick, H.M., McLaine, P.N., Farant, J.P., 1982. A case of accidental inorganic mercury poisoning. J. Anal. Toxicol. 6, 120–122.
Santos, E.C., Jesus, I.M., Brabo, E.S., Loureiro, E.C., Mascarenhas, A.F., Weirich, J., Camara, V.M., Cleary, D., 2000. Mercury exposures in riverside Amazon communities in Para, Brazil. Environ. Res. 84, 100–107.
Santos, E.C., Jesus, I.M., Camara, V., de, M., Brabo, E.S., Loureiro, E.C., Mascarenhas, A.F., Weirich, J., Luiz, R.R., Cleary, D., 2002. Mercury exposures in Munduruku Indians from the community of Sai Cinza, State of Para, Brazil. Environ. Res. 90, 98–103.
Satoh, H., 2000. Occupational and environmental toxicology of mercury and its compounds. Ind. Health 38, 153–164.
Schober, S.E., Sinks, T.H., Jones, R.L., Bolger, P.M., McDowell, M., Osterloh, J., Garett, E.S., Canady, R.A., Dillon, C.F., Sun, Y., Joseph, C.B., Mahaffey, K.R., 2003. Blood mercury levels in U.S. children and women of childbearing age, 1999–2000. J. Am. Med. Assoc. 289, 1667–1674.
Shafer, T.J., Meacham, C.A., Barone Jr., S., 2002. Effects of prolonged exposure to nanomolar concentrations of methylmercury on voltage-sensitive sodium and calcium currents in PC12 cells. Brain Res. Dev. Brain Res. 136, 151–164.
Sirois, J.E., Atchison, W.D., 1996. Effects of mercurials on ligand- and voltage-gated ion channels: a review. Neurotoxicology 17, 63–84.
Snapp, K.R., Boyer, D.B., Peterson, L.C., Svare, C.W., 1989. The contribution of dental amalgam to mercury in blood. J. Dent. Res. 68, 780–785.
Snodgrass, W., Sullivan, J.B., Rumack, B.H., Hashimoto, C., 1981. Mercury poisoning from home gold ore processing. J. Am. Med. Assoc. 246, 1929–1931.
Solis, M.T., Yuen, E., Cortez, P.S., Goebel, P.J., 2000. Family poisoned by mercury vapor inhalation. Am. J. Emerg. Med. 18, 599–602.
Soni, J.P., Singhania, R.U., Bansal, A., Rathi, G., 1992. Acute mercury vapor poisoning. Indian Pediatr., 365–368.
Soo, Y.O., Chow, K.M., Lam, C.W., Lai, F.M., Szeto, C.C., Chan, M.H., Li, P.K., 2003. A whitened face woman with nephrotic syndrome. Am. J. Kidney Dis. 41, 250–253.
Sorensen, F.W., Larsen, J.O., Eide, R., Schionning, J.D., 2000. Neuron loss in cerebellar cortex of rats exposed to mercury vapor: a stereological study. Acta Neuropathol. 100, 1000–1995.
Stajich, G.V., Lopez, G.P., Harry, S.W., Sexson, W.R., 2000. Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants. J. Pediatr. 136, 679–681.
Stehr-Green, P., Tull, P., Stellfeld, M., Mortenson, P.B., Simpson, D., 2003. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. Am. J. Prev. Med. 25, 101–106.
Stein, J., Schettler, T., Wallinga, D., Valenti, M., 2002. In harm's way: toxic threats to child development. J. Dev. Behav. Pediatr. 23, S13–S22.
Stern, A.H., Gochfeld, M., 1999. Effects of methylmercury exposure on neurodevelopment. J. Am. Med. Assoc. 281, 896–897.
Stewart, P.W., Reihman, J., Lonky, E.I., Darvill, T.J., Pagano, J., 2003. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol. Teratol. 25, 11–22.
Sweet, L.I., Zelikoff, J.T., 2001. Toxicology and immunotoxicology of mercury: a comparative review in fish and humans. J. Toxicol. Environ. Health, Part B 4, 161–205.
Takahashi, Y., Tsurutaa, S., Hasegawa, J., Kameyam, Y., Yoshida, M., 2001. Release of mercury from dental amalgam fillings in pregnant rats and distribution of mercury in maternal and fetal tissues. Toxicology 163, 115–126.
Takahashi, Y., Tsurutaa, S., Arimotoa, M., Tanakab, H., Yoshida, M., 2003. Placental transfer of mercury in pregnant rats which received dental amalgam restorations. Toxicology 185, 23–33.
Thomas, D.J., Smith, J.C., 1982. Effects of coadministered low-molecular-weight thiol compounds on short-term distribution of methyl mercury in the rat. Toxicol. Appl. Pharmacol. 62, 104–110.
Tlacuilo-Parra, A., Guevara-Gutierrez, E., Luna-Encinas, J.A., 2001. Percutaneous mercury poisoning with beauty cream in Mexico. J. Am. Acad. Dermatol. 45, 6.
Tsubaki, T., Irukayama, K. (Eds.), 1977. Minamata Disease: Methylmercury Poisoning in Minamata and Niigata, Japan. Elsevier, New York.
U.S. Environmental Protection Agency, 1997. Mercury Study Report to Congress. Document EPA-452/R-97-007. Research Triangle Park, North Carolina.
Vahter, M., Akesson, A., Lind, B., Bjors, U., Schutz, A., Berglund, M., 2000. Longitudinal study of methylmercury and inorganic mercury in blood and urine of pregnant and lactating women, as well as in umbilical cord blood. Environ. Res. 84, 186–194.
Verstraeten, T., Davis, R.L., DeStefano, F., Lieu, T.A., Rhodes, P.H., Black, S.B., Shinefield, H., Chen, R.T., 2004. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. Pediatrics 112, 1039–1048.
Vimy, M.J., Takahashi, Y., Lorscheider, F.L., 1990. Maternal–fetal distribution of mercury (203 Hg) released from dental amalgam fillings. Am. J. Physiol. 258, R939–R945.
Vimy, M.J., Hooper, D.E., King, W.W., Lorscheider, F.L., 1997. Mercury from maternal "silver" tooth fillings in sheep and human breast milk. A source of neonatal exposure. Biol. Trace Elem. Res. 56, 142–143.
Vroom, F.Q., Greer, M., 1972. Mercury vapor intoxication. Brain 95, 305–318.
Warfvinge, K., 2000. Mercury distribution in the neonatal and adult cerebellum after mercury vapor exposure of pregnant squirrel monkeys. Environ. Res. 83, 93–101.
Warfvinge, K., Bruun, A., 2000. Mercury distribution in the squirrel monkey retina after in utero exposure to mercury vapor. Environ. Res. 83, 102–109.
Weinstein, M., Bernstein, S., 2003. Pink ladies: mercury poisoning in twin girls. Can. Med. Assoc. J. 168, 200.
Weldon, M.M., Smolinski, M.S., Maroufi, A., Hasty, B.W., Gilliss, D.L., Boulanger, L.L., Balluz, L.S., Dutton, R.J., 2000. Mercury poisoning associated with a Mexican beauty cream. West J. Med. 173, 15–18.
Wendroff, A.P., 1995. Magico-religious mercury use and cultural sensitivity. Am. J. Public Health 85, 409–410.
White, R.F., Dahl, D.F., Grandjean, P., 1998. Development and field testing of a neuropsychological test battery to assess the effects of methylmercury exposure in the Faroe Islands. Proceedings of the International Symposium on Assessment of Environmental Pollution and Health Effects of Methylmercury. Kumamoto University, Kumamoto, Japan.
Williams, J.E., Schram, C.F., 1937. Acute mercurial poisoning. Ind. Med. 6, 490–491.
Wood, J.M., Kennedy, F.S., Rosen, C.G., 1968. Synthesis of methyl-mercury compounds by extracts of a methanogenic bacterium. Nature 220, 173–174.

World Health Organization (WHO), 1990. MethylmercuryEnviron. Health Criteria, vol. 101. World Health Organization, Geneva.

World Health Organization (WHO), 1991. Inorganic mercuryEnviron. Health Criteria, vol. 118. World Health Organization, Geneva.

Yoshida, M., Satoh, M., Shimada, A., Yasutake, A., Sumi, Y., Tohyama, C., 1999a. Pulmonary toxicity caused by exposure to mercury vapor is enhanced in metallothionein-null mice. Life Sci. 64, 1861–1877.

Yoshida, M., Satoh, M., Yasutake, A., Shimada, A., Sumi, Y., Tohyama, C., 1999b. Distribution and retention of mercury in metallothionein-null mice after exposure to mercury vapor. Toxicology 139, 129–136.

Yoshida, M., Satoh, M., Shimada, A., Yamamoto, E., Yasutake, A., Tohyama, C., 2002. Maternal-to-fetus transfer of mercury in metallothionein-null pregnant mice after exposure to mercury vapor. Toxicology 175, 215–222.

Zayas, L.H., Ozuah, P.O., 1996. Mercury use in espiritismo: a survey of botanicas. Am. J. Public Health 86, 111–112.