

HEALTH EFFECTS

REVIEW

Methylmercury

Introduction

Methylmercury (MeHg) is a neurotoxicant with well-defined neuropathological and developmental effects. Seafoods, including tuna, are often contaminated with MeHg. This has raised questions about the safety of consuming such foods, especially for high-risk populations, including pregnant women and children. Given the NHANES exposure data and numbers of children born in the U.S. annually, Mahaffey et al. (2004) estimated that 300,000 infants born in 2000 may have been exposed to greater than or equal to 58 micrograms/liter of MeHg *in utero* (the USFDA recommended limit).

The concern about MeHg contamination has raised vigorous discussion of the nutritional benefits of seafood consumption versus risks associated with MeHg exposure. A summary of the existing studies and known effects of MeHg appeared in Volume I of this publication in 1996. In the intervening 8 years, several studies of populations of children exposed to MeHg *in utero* and during development have published new data, and updated reference doses for exposure to the toxicant have been proposed. In addition, new data have appeared linking MeHg exposure in adulthood to cardiovascular risk factors. In this summary, we will review the data that established MeHg as a neurotoxicant, provide an update on the newest findings on health effects of MeHg, and summarize the debate on the optimal reference dose for MeHg exposure.

Methylmercury Neurotoxicity

The potent neurotoxicity of MeHg was dramatically demonstrated in the mid-20th century in Japan and Iraq. In the 1950s, the occurrence of clinical methylmercury poisoning producing acute neurological symptoms and death in adults and children as well as congenitally based disorders in children that resembled cerebral palsy was reported in the Minamata Bay area of Japan (Harada, 1978). These cases were found to be associated with the consumption of seafood from Minamata Bay that had been contaminated by mercury from a chloralkali plant. The clinical syndrome associated with these exposures became known as "Minamata disease." The clinical manifestations of poisoning associated with this episode highlighted the special sensitivity of infants and unborn children to the nervous system effects of MeHg: children with severe symptoms were born to mothers with few or no symptoms of MeHg poisoning. A second episode of poisoning occurred in 1960, in Iraq when contaminated wheat seed was consumed by approximately 1000 people. Prenatal exposure was associated with early death and with obvious and subtle motor deficits (Bakir et al., 1973).

These episodes demonstrated the remarkable developmental curve of MeHg neurotoxicity. With regard to the clinical symptoms manifested by affected individuals, prenatal exposure was associated with the most severe outcomes,

adult exposure with the mildest. These clinical pictures were reflected in the neuropathological abnormalities reported for the victims' brains. At autopsy, the brains of individuals from Japan and Iraq with prenatal exposure showed widespread lesions and abnormalities in neuronal migration during brain development, early childhood exposure was associated with numerous widespread lesions, and adult Minamata disease victims had focal lesions mostly localized to the posterior portions of the brain and the cerebellum (Choi, 1989).

Following the Iraq poisoning episode and based on outcome data from health studies of the Iraqi victims, the World Health Organization (WHO) concluded that hair levels of 10-20 ppm in mothers were associated with a minimal effect risk of 5%. This reference level was used for regulatory purposes for many years but came under scrutiny following studies that examined effects of MeHg at levels below which individuals manifest symptoms of Minamata disease but at which subtle alterations in central nervous system function may occur. Subtle effects of MeHg exposure in apparently healthy individuals have been the focus of recent studies.

Cohort Studies on the Effects of Methylmercury to a Child's Central Nervous System

Seychelle Islands studies

A longitudinal study of MeHg effects among 779 children residing in the Seychelle Islands was begun in 1987 (Myers et al., 2003). Fish is a staple in their diet and the Seychellois consume an array of oceanic fish that have been calculated to have a mean MeHg content of 0.3 micrograms/gram, which is lower than the measured MeHg content in the fish and whale consumed by the other cohorts discussed in this review. Central nervous system function was examined in these children at 6.5 months, when no adverse relationships between maternal MeHg hair levels at birth and children's test scores were found (Myers et al., 1995). At age 19 and 29 months, 738 of the children were again examined (Davidson et al., 1995). Maternal hair levels for this group ranged from 0.5-26.7 ppm (mean=5.9 ppm). MeHg exposure levels were not found to be related to performance on omnibus scores of infant development, though decreased activity was associated with increased exposure among boys. At age 66 months, 711 cohort children were again examined without finding adverse relationships between maternal hair levels of MeHg at birth and cognitive outcomes (Davidson et al., 1998). Examinations of 643 cohort children at age 9 were generally negative, with the exception of decreased performance on a manual motor dexterity test with the non-dominant hand among males only (Davidson et al., 2000).

Faroe Islands studies

A birth cohort of 1022 children was generated in the Faroe Islands in 1986-1987 and has been followed since with

regard to MeHg exposure and health outcomes. This cohort was exposed to MeHg prenatally through maternal consumption of fish and whale meat. No relationships between prenatal exposure to methylmercury and developmental milestone measures were seen in early childhood (Grandjean et al., 1995) and there were no observed cases of Minamata disease. However, comprehensive assessments at age 7 showed significant relationships between cord blood mercury levels and neuropsychological test performance, particularly in the domains of language, attention and memory when controlling for relevant confounders. These findings held when data were examined only for children whose cord blood levels were less than 10 ppm (Grandjean et al., 1997). Analyses of the data were repeated in order to examine possible confounding effects of exposure to polychlorinated biphenyls (PCBs). Results showed no effects of PCBs except in the highest tertile of MeHg exposure (Grandjean et al., 2001). The children were again examined at age 14, when brainstem auditory evoked potential results suggested continued effects of prenatal exposure on brain function (Murata et al., 2004). Results of neuropsychological testing at age 14 have not been reported. Investigations with the Faroese cohort have also revealed relationships between prenatal MeHg exposure and the autonomic nervous system indicators of blood pressure and heart rate variability.

Other studies

An investigation of the relationship between current hair mercury levels in children and performance on neuropsychological tests was conducted in four Amazonian communities in Brazil, where MeHg exposure is associated with the consumption of fish contaminated by mercury used in gold mining (Grandjean et al., 1999). Of the 420 children aged 7-12 in these communities, 351 were examined. Exposures were high in 3 of the communities: 80% of the children had hair levels above 10 ppm. When dose-effect data were evaluated from all 4 communities, higher MeHg levels were associated with poorer performance on cognitive and motor tasks. Analysis of data from the community with the lowest MeHg exposure (only 2/105 children had hair levels above 10), significant inverse relationships between MeHg levels and performance on tests of visuospatial and motor function remained.

A study carried out in French Guiana examined 156 children from three Amerindian communities with varying levels of exposure (Cordier et al., 2002). In the community with the highest exposure levels (mean about 12 ppm), higher maternal hair levels of MeHg were associated with increased tendon reflexes, decreased leg coordination, and poorer performance on the same test of visuospatial function (drawings of designs) used in the Amazonian study described above. Relationships were more pronounced among boys.

The 1996 review of MeHg effects in this publication described a study carried out in New Zealand that evaluated developmental effects in 31 children at age 4 and 61 children at age 7-8 whose mothers' hair MeHg level exceeded 6 ppm (Kjellstrom et al., 1986, 1989). The investigators concluded that developmental effects of MeHg can be observed in the 13-15 ppm range of maternal hair mercury at the child's birth. This study was used in the analyses leading to new suggestions for a reference dose (RfD) for MeHg exposure described below, but no new publications have appeared on the cohort since 1996.

Cardiovascular Effects

Mercury exposure has also been suspect as a possible risk

factor for diminished cardiovascular health in adults. An investigation of 684 men with first myocardial infarct and 724 controls from Europe and Israel showed that toenail mercury levels were 15% higher in the patients than the controls (Guallar et al., 2002). However, another study published at the same time produced contradictory results, concluding that toenail mercury levels were not associated with coronary artery disease in 470 cases and 470 matched controls selected from a cohort of 33,737 health professionals (Yoshizawa et al., 2002). Given the reported increases in blood pressure and heart rate variability associated with mercury exposure, the associations between mercury exposure and cardiovascular health deserve continued study.

Reference Dose Deliberations

The existing EPA-recommended RfD for MeHg is 0.1mcg/kg/day (Rice et al., 2003). This dosage is based on benchmark calculations from the National Research Council (NRC, 2000) and a "safety factor" of 10. As the RfD was being developed, there was considerable disagreement among US governmental regulatory agencies about whether a safety factor of 3 or 10 was more appropriate. The benchmark analyses utilized data from three of the studies described above (Seychelles, Faroes and New Zealand studies).

The statistical modeling used to quantify the health effects, uncertainties about hair to blood and maternal blood to cord blood ratios, uncertainties about the degree of variability among individuals in these ratios, and the paucity of knowledge on which to base benchmark analyses for other MeHg-related health outcomes such as cardiovascular disease all require further consideration. (Rice, 2003; Rice et al., 2003).

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