

EXCERPT FROM MERCURY STUDY REPORT TO CONGRESS

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HEALTH EFFECTS OF MERCURY AND MERCURY COMPOUNDS

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4. SUSCEPTIBLE POPULATIONS

A susceptible population is a group who may experience more severe adverse effects at comparable levels or adverse effects at lower exposure levels than the general population. The greater response of these sensitive subpopulations may be a result of a variety of intrinsic or extrinsic factors. Volume V describes populations that may be at increase risk because of higher exposure to mercury and mercury compounds. Additional factors that may be important include, but are not limited to, the following: an impaired ability of the detoxification, excretory, or compensatory processes in the body to protect against or reduce toxicity; differences in physiological protective mechanisms (e.g., blood brain barrier); or unique toxic reactions that are specific to the genetic makeup, developmental stage, health status, gender or age of the individual.

The nervous and renal systems are the primary targets for mercury-induced toxicity. Data are also available indicating some effects to the respiratory, cardiovascular, gastrointestinal, hematologic, immune, and reproductive systems. The developing organism appears to be particularly sensitive to methylmercury exposure. In addition, it is probable that individuals with preexisting damage or disease in target organs for mercury-induced toxicity may experience more severe effects upon exposure to mercury. The populations listed below may be highly susceptible to mercury toxicity.

- Developing Organisms. Data from epidemic poisonings in Japan (Harada 1978) and Iraq (Marsh et al. 1987) indicate that infants exposed *in utero* to methylmercury developed marked neurological development delays while their mothers experienced little or no overt signs of toxicity. Data indicate that the developing fetus may be 5 to 10 times more sensitive than the adult (Clarkson, 1992). This difference in sensitivity is believed to be due, in part, to the high sensitivity of developmental processes (i.e., cellular division, differentiation, and migration) to disruption by mercury (Choi et al. 1978; Sager et al. 1982). One factor that may account for this difference in sensitivity is the presence of an incomplete blood brain barrier in the fetus. Another important factor may be the lack of methylmercury excretion in the fetus (Grandjean et al. 1994).
- Age - Infants and Other Age Groups. Available data indicate that neonates are at increased risk to inorganic mercury and methylmercury. Both inorganic and organic forms of mercury are excreted in breast milk (Sundberg and Oskarsson 1992; Yoshida et al. 1992; Grandjean et al. 1994); thus, neonates in an exposed population may experience increased mercury exposure. Animal data for rats indicate that suckling infants retain a higher percentage of ingested inorganic mercury than do adults (Kostial et al. 1978). The most significant difference in organ retention (neonates > adults) was methylmercury in the brain following exposure to methylmercury (Yang et al. 1973; Kostial et al. 1978) and inorganic mercury retained in the kidney following exposure to elemental mercury (Yoshida et al. 1992). These differences may be associated with an increased absorption of mercury with a milk diet, a decrease in excretion, or an incomplete blood brain barrier (Kostial et al. 1978, Grandjean et al. 1994).

Signs of toxicity may begin to be manifested several years after the cessation of dosing, possibly related to subclinical effects being unmasked by aging. Rice (1989b) dosed monkeys with methylmercury from birth to 6.5-7 years of age. Although there were no overt signs of neurotoxicity during dosing, neurological deficits were observed at 13

years of age, 6-7 years following cessation of exposure. Similarly, a small human population with Minamata disease has been identified in Japan as experiencing new or worsening neurological effects a few years following termination of mercury exposure. This late-onset Minamata disease may be related to several factors including aging (Igata 1993).

- Gender. Sex-related differences in mercury toxicokinetics and sensitivity to mercury have been observed, although data indicate that the more sensitive sex may differ by species and strain. Using death as the critical endpoint, in one strain of mice, C57BL/6N, males were less sensitive to methylmercury following daily dosing than females while, in contrast, male mice were more sensitive than females in another strain, BALB/cA (Yasutake and Hirayama 1988). In humans, although the ratio of males to females with Minamata disease has been reported to be 1.2:1, the ratio of deaths was recorded at 1.8:1 (Tamashiro et al. 1984).

Other studies are in general agreement that male rats (Thomas et al. 1986) and mice (Nielsen and Andersen 1991a, 1991b) eliminate mercury faster and have lower tissue levels than females following dosing with methylmercury. Part of the difference in whole-body retention of mercury in methylmercury-exposed mice has been associated with varying degrees of deposition of mercury in the carcass, including the skin and hair (Nielsen and Andersen 1991b). This difference is thought to be due in part to differences in glutathione metabolism and renal excretion of mercury, which is affected by the hormonal status of testosterone (Nielsen et al. 1994). Hirayama et al. (1987) have reported that the toxicokinetics of methylmercury in castrated male mice was very similar to that in female mice, and that the male pattern of methylmercury toxicokinetics could be restored by testosterone treatment. Such differences were not observed in a small set of similarly tested human volunteers (Miettinen et al. 1971).

- Dietary Insufficiencies of Zinc, Glutathione, or Antioxidants. Mercury has been suggested to cause tissue damage by increasing the formation of reactive oxygen species and activation of lipoperoxidation, calcium-dependent proteolysis, endonuclease activity, and phospholipid hydrolysis (Ali et al. 1992; LeBel et al. 1990, 1992; Gstraunthaler et al. 1983; Verity and Sarafian 1991). Zinc, glutathione, and antioxidant deficiencies would be expected to exacerbate mercury-induced damage by limiting cellular defenses against the oxidative processes. Animal data support the importance of zinc, glutathione, and antioxidants in limiting mercury-induced damage (Fukino et al. 1992; Girardi and Elias 1991; Yamini and Sleight 1984) (see also Section 5, Interactions).
- Predisposition for Autoimmune Glomerulonephritis. Autoimmune glomerulonephritis is a form of renal toxicity characterized by proteinuria, deposition of immune material (i.e., autoantibodies and complement C3) in the renal mesangium and glomerular blood vessels and glomerular cell hyperplasia (Bigazzi 1992; Goldman et al. 1991; Mathieson 1992). Limited human data suggest that certain individuals may develop this autoimmune response when exposed to inorganic or elemental mercury (Cardenas et al. 1993; Langworth et al. 1992b; Tubbs et al. 1982). While the etiology of this syndrome has not been completely elucidated, data from susceptible and resistant strains of animals indicate that susceptibility is governed by both major histocompatibility complex (MHC)

genes and non-MHC genes (Aten et al. 1991; Druet et al. 1978; Hultman and Enestrom 1992; Hultman et al. 1992; Michaelson et al. 1985; Sapin et al. 1984).

- Predisposition for Acrodynia. Acrodynia, also known as "pink disease," is a hypersensitive response following exposure to elemental or inorganic mercury and is characterized by the following signs and symptoms: irritability; marked mood swings; restlessness; itching; flushing, swelling, and/or desquamation of the palms of the hands and soles of the feet (the tip of the nose, ears, and cheeks may also be affected); excessive perspiration; loss of appetite; tachycardia; hypertension; joint pains and muscle weakness; photophobia; and sleeplessness. Acrodynia, which is more likely related to exposure level rather than any inherent, genetic sensitivity, rarely occurs in the general population.

Limited reports indicate that acrodynia has been almost exclusively observed in children, affecting approximately 1 in 500 exposed children (Blondell and Knott 1993; Warkany and Hubbard 1953). This disease was recently observed in a 4-year-old Michigan boy who was exposed to mercury vapor released from paint in which mercury had been used as a fungicide (Aronow et al. 1990). In this case, family members (i.e., both parents and two siblings) were also exposed to the mercury vapors but remained asymptomatic (Aronow et al. 1990). This case study supports the hypothesis that there is no genetic predisposition to acrodynia.

Acrodynia was more frequently observed in the past when mercury-containing laxatives, worming medications, teething powders and diaper rinses were widely used (Gotelli et al. 1985; Warkany and Hubbard 1953). The physiological basis for this hypersensitivity has not been identified. It does not appear, however, to be an allergic reaction to mercury or to occur in the most highly exposed individuals (Warkany and Hubbard 1953).