540186042

United States
Environmental Protection
Agency

Office of Emergency and
Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
Assessment Office
Cincinnati OH 45268

Superfund

EPA

HEALTH EFFECTS ASSESSMENT FOR MERCURY

Do not remove. This document
should be retained in the EPA
Region 5 Library Collection.

HW
EPAX
8605-
0087

EPA/540/1-86-042
September 1984

HEALTH EFFECTS ASSESSMENT FOR MERCURY

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

The information in this report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with mercury. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Mercury. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-058. NTIS PB 81-117699.

U.S. EPA. 1983b. Reportable Quantity for Mercuric Nitrate. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Mercury Health Effects Update. Health Issue Assessment. Final Report. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-84-019F. NTIS PB 85-123925.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The consequences of human oral exposure to methyl mercury are well documented. U.S. EPA (1980b) estimated an ADI of 20 μg Hg/day for waterborne methyl mercury. New data have not emerged which would suggest modification of this estimate. Therefore, 20 μg/day is proposed as the AIS and AIC value for oral exposure. This value assumes the contribution by inhalation is <10 μg/day. This value is applicable to alkyl mercury exposure and to mixed alkyl-inorganic exposures. A CS of 59.4 was derived for mercury from methylmercury ingested by pregnant mothers, resulting in retarded psychomotor development in their infants.

Data concerning inhalation exposure to alkyl mercury compounds are limited and consist primarily of occupational reports. An AIS and AIC for inhalation of 7.14 μg/day is suggested based on the TLV. This estimate should be reviewed as more complete data become available.

No subchronic oral exposure data were located for inorganic mercury compounds. A single chronic study where rats were fed diets containing mercuric acetate was located. Based on this study, an oral AIS and AIC of 140 μg/day were estimated. This value is applicable solely to circumstances where exposure is limited to inorganic mercury salts. These estimates should be reviewed when more complete data are available.

Information concerning inhalation exposure to inorganic mercury compounds is also extremely limited. Some data are available from occupational exposures. Using the TLV, an AIS of 35.7 μg/day and an AIC of 3.6 μg/day have been estimated. Again, these estimates should be reviewed when additional data are available. A CS of 42.4 was calculated for effects on the CNS observed in workers occupationally exposed to mercuric nitrate.

ACKNOWLEDGEMENTS

TECHNICAL REVIEW

Scientists from the following U.S. EPA offices provided review comments for this document series:

Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

EDITORIAL REVIEW

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

TECHNICAL SUPPORT SERVICES

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112.

TABLE OF CONTENTS

	Page
1. ENVIRONMENTAL CHEMISTRY AND FATE	1
2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	4
2.1. ORAL	4
2.1.1. Inorganic Mercury and Salts	4
2.1.2. Methylmercury	4
2.2. INHALATION	5
2.2.1. Inorganic Mercury	5
2.2.2. Methylmercury	5
3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	6
3.1. SUBCHRONIC	6
3.1.1. Oral	6
3.1.2. Inhalation	7
3.2. CHRONIC	8
3.2.1. Oral	8
3.2.2. Inhalation	12
3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS	14
3.3.1. Oral	14
3.3.2. Inhalation	15
3.4. TOXICANT INTERACTIONS	15
4. CARCINOGENICITY	16
4.1. HUMAN DATA	16
4.2. BIOASSAYS	16
4.3. OTHER RELEVANT DATA	16
4.3.1. Inorganic Mercury	16
4.3.2. Methylmercury	16
4.4. WEIGHT OF EVIDENCE	16
5. REGULATORY STANDARDS AND CRITERIA	17

TABLE OF CONTENTS (cont.)

Page

6. RISK ASSESSMENT 18

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS) 18

6.1.1. Oral. 18
6.1.2. Inhalation. 19

6.2. ACCEPTABLE INTAKE CHRONIC (AIC). 20

6.2.1. Oral. 20
6.2.2. Inhalation. 21

6.3. CARCINOGENIC POTENCY (q_1*) 22

7. REFERENCES. 23

APPENDIX A: Summary Table for Inorganic Mercury. 36

APPENDIX B: Summary Table for Methylmercury. 37

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CNS	Central nervous system
CS	Composite score
GI	Gastrointestinal
LC_{25}	Concentration lethal to 25% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Mercury is a metal belonging to group II B of the periodic table. Metallic mercury exists as a liquid at room temperature. In the environment, mercury exists in three oxidation states: 0 (elemental), +1 (mercurous compounds) and +2 (mercuric compounds). Metallic mercury (CAS No. 7439-97-6) has a vapor pressure of 1.2×10^{-3} mm Hg at 20°C and a water solubility of 81.3 µg/ℓ at 30°C (Callahan et al., 1979). In the +1 state, the mercurous salts are not very soluble in water. For example, the solubility of mercurous chloride is 2 mg/ℓ at 25°C, and the solubility of mercurous sulfate is 600 mg/ℓ at 25°C (Weast, 1980). In the +2 state, mercury salts are more water soluble. The solubility of mercuric chloride and mercuric acetate are 69 g/ℓ at 20°C and 250 g/ℓ at 10°C, respectively; however, mercuric sulfide has a water solubility of only 0.01 mg/ℓ at 18°C (Weast, 1980).

Besides a variety of inorganic compounds, mercury forms a number of compounds with organic ligands. In these compounds, mercury is attached to at least one carbon atom by a covalent bond. These compounds are toxicologically and environmentally significant. Methylmercury, ethylmercury, phenylmercury and alkoxyphenylmercury are some of the prominent compounds belonging to the class of organomercuric compounds.

Mercury is expected to be present in the atmosphere mainly as Hg(0) from electrical and chloroalkali industries and the burning of fossil fuels. Other anthropogenic sources of atmospheric mercury are organomercuric compounds, such as aryl-, alkoxyaryl-, methyl- and ethylmercury compounds used as fungicides (U.S. EPA, 1980b). It is likely that dialkyl- or diarylmercury will be converted to Hg(0) by photochemical reactions in the

atmosphere. The alkyl- and phenylmercurial salts, however, may photodecompose into simple inorganic mercurous salts, as shown below (Zepp et al., 1973; Callahan et al., 1979):

$$R\ Hgx \xrightarrow{hv} R\bullet + \bullet Hgx$$

$$2\bullet Hgx \rightarrow Hg_2x_2$$

The residence time of mercury in the atmosphere has been calculated to be 5.7 years (Katsuniko and Takumi, 1976). Mercury is removed from the atmosphere mainly through precipitation. During the removal of Hg(0) from the atmosphere by rainwater, it is probably oxidized to Hg(+1) in the presence of oxygen (U.S. EPA, 1980b).

The aquatic fate of mercury and compounds has been studied extensively. Photolysis, chemical speciation, volatilization, sorption and biotransformation are all important processes in aquatic media. The relative importance of these processes in determining the final aquatic fate of mercury remains uncertain. Adsorption onto the surface of particulate matter and subsequent sedimentation probably constitutes the most important mercury removal mechanism in the aquatic system (Callahan et al., 1979). A part of the precipitated mercury may be transformed into organic mercurial compounds through biotransformation and may reenter the aquatic phase.

Mercury is strongly bound to soil and is attached predominantly to soil organic matter. Therefore, the mobility of mercury and compounds in soil is minimal even in soils contaminated by mercury fungicides. The probability of groundwater contamination with mercury through soil leaching appears unlikely; however, the mobility of mercury in soils may be enhanced by leachates from municipal landfills (U.S. EPA, 1980b).

The BCF values for mercury in aquatic organisms have been determined by several investigators. In edible aquatic organisms, the BCF values vary from 250 for muscle of plaice (flounder) to 63,000 for fathead minnows (*Pimephales promelas*) (U.S. EPA, 1980b).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

2.1.1. Inorganic Mercury and Salts. Metallic mercury appears to be poorly absorbed from the GI tract. Bornmann et al. (1970) administered gram quantities of metallic mercury orally to animals (species unspecified). In a reanalysis of this study, Friberg and Nordberg (1973) estimated that <0.01% of the administered dose was absorbed from the GI tract. Suzuki and Tonaka (1971) reported some increase in blood levels in individuals who accidentally ingested several grams of metallic mercury. The literature contains numerous reports of individuals who consumed gram quantities of metallic mercury without developing any ill effects (U.S. EPA, 1980b).

Rahola et al. (1971) administered mercuric nitrate bound to calf liver protein (~6 μg mercury/dose) to eight volunteers and an acid solution of mercuric nitrate to two volunteers. GI absorption of the inorganic mercury was estimated to be <15%. This is in agreement with values reported in experimental animals (Clarkson, 1971). GI absorption has been estimated to be greater in suckling animals than in mature ones (Kostial et al., 1978).

2.1.2. Alkyl Mercury. Aberg et al. (1969) and Miettinen (1973) have administered methylmercury to volunteers as a simple salt in solution or bound to protein. The methylmercury was essentially completely absorbed in either form. High rates of absorption have also been observed in volunteers who consumed contaminated tuna fish for several days (Turner et al., 1974, 1975) and in individuals who ate homemade bread contaminated with a fungicide containing methylmercury (Shahristani et al., 1976).

2.2. INHALATION

2.2.1. Inorganic Mercury. Teisinger and Fiserova-Bergerova (1965) proposed that the bronchioles and larger airways of the lungs were the major sites of absorption of metallic mercury, but Berlin et al. (1969) found that the predominant sites of absorption were the alveoli. A number of studies have indicated that ~80% of the inhaled vapor from metallic mercury is absorbed by humans (Teisinger and Fiserova-Bergerova, 1965; Nielsen-Kudsk, 1965; Hurch et al., 1976).

Morrow et al. (1964) exposed dogs to a mercuric oxide aerosol with a mean diameter of 0.16 μm. They estimated that 45% of the administered dose was absorbed within 24 hours. No information was found on the pulmonary absorption of inorganic mercury aerosols in other species.

2.2.2. Alkyl Mercury. Pertinent data regarding the pulmonary absorption of alkyl mercury could not be located in the available literature. The U.S. EPA Task Group on Metal Accumulation (1973) suggested that the retention of inhaled alkylmercurial compounds would probably be ~80%, based on diffusibility and lipid solubility.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral.

3.1.1.1. INORGANIC MERCURY -- No reports on the subchronic toxicity of orally administered metallic mercury were located in the available literature. The subchronic oral toxicity of inorganic mercury salts in man has not been described; however, the lethal oral dose of $HgCl_2$ has been estimated to be 1-4 g (Gleason et al., 1957).

Clarkson (1977) found that repeated daily doses of Hg^{++} (species and compound unspecified) resulted in induction of metallothionein synthesis. Since metallothionein is involved in the detoxification of Hg^{++} ions (Piotrowski et al., 1973), much higher concentrations of inorganic mercury can be tolerated after chronic exposure.

3.1.1.2. ALKYL MERCURY -- A number of reviews have indicated both quantitative and qualitative differences in methylmercury poisoning following prenatal and postnatal exposure. Subchronic exposure to methylmercury has occurred in humans consuming contaminated fish in Minamata (Katsuna, 1968) and Niigata, Japan (Tsubaki and Irukayama, 1977), and homemade bread made from seed grain that had been treated with a methylmercury fungicide in rural Iraq (Bakir et al., 1973; Mufti et al., 1976; Shahristani et al., 1976; Clarkson et al., 1976; WHO, 1976). Cases of mercury poisoning have also been reported following occupational exposures of 3-4 months, but the route and extent of exposure have not been well defined (Hunter et al., 1940; Hunter and Russell, 1954; Edwards, 1865). In all of these cases, the major signs of toxicity were paresthesia of the extremities, impaired peripheral field of vision, slurred speech and unsteadiness of gait and limbs. Maximum severity of symptoms occurred several weeks after the end of exposure.

Other investigators have reported a delayed onset of symptoms in humans and other primates. Evans et al. (1977) reported an inverse relationship between steady-state blood levels of methylmercury and the length of the latent period in monkeys, with a latent period of up to 1 year at the lowest doses. Tsubaki et al. (1978) reported that four patients developed mild nonspecific symptoms several years after the Niigata outbreak. Maximum hair concentrations were between 50 and 300 μg Hg/g hair.

Several investigators have reported cases of psychomotor retardation in children exposed to methylmercury *in utero*, even though the mothers were unaffected or displayed only transient effects (Engleson and Herner, 1952; Harada, 1968; Takeuchi, 1968; Snyder, 1971; Pierce et al., 1972; Amin-Zaki et al., 1974a,b; Choi et al., 1977). Marsh et al. (1977) found significant differences in delayed developmental milestones, the histories of seizures and the number of infants having multiple signs of poisoning, in infants of mothers who had maximum hair concentrations of 99-384 μg Hg/g compared with infants from mothers with maximum hair concentrations of ≤85 μg Hg/g.

3.1.2. Inhalation. The World Health Organization (WHO, 1976) investigated the data from the mercury poisoning outbreaks in Japan and Iraq and studied fish-eating populations in other parts of the world. They attempted to correlate mercury concentrations in hair and blood with the incidences and severity of neurotoxicity, and concluded that blood levels of 200-500 ng/mℓ and concentrations of 50-125 μg/g in hair correlated with the onset of neurologic signs in 3-8% of a population. These concentrations in blood and hair appeared to correspond to a long-term daily intake of methylmercury at 37 μg/kg/bw. The National Academy of Sciences (NAS, 1978) reviewed the work of WHO (1976) and endorsed their conclusions.

3.1.2.1. INORGANIC MERCURY -- The effects of mercury vapor on human health have been reviewed extensively (Friberg and Vostal, 1972; NIOSH, 1973; Friberg and Nordberg, 1973; Nordberg, 1976; WHO, 1976). Exposure to concentrations >1 mg Hg/m³ results in damage to lung tissue and acute mercurial pneumonitis. At lower concentrations, the effects observed primarily involved the CNS (Milne et al., 1970).

Baranski and Szymczyk (1973) found that women working in dental offices in Lithuania, where mercury vapor concentrations reached a maximum of 0.08 mg/m³, had an increased incidence of abortion and mastopathy related to duration of time on the job. A number of case reports have also related exposure to mercury vapor with menstrual disturbances and spontaneous abortions (Baranski and Szymczyk, 1973; Derobert and Tara, 1950).

3.1.2.2. ALKYL MERCURY -- Pertinent data regarding the subchronic toxicity of alkyl mercury vapors could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral.

3.2.1.1. INORGANIC MERCURY AND SALTS -- Pertinent data regarding the chronic oral toxicity of metallic mercury could not be located in the available literature. Fitzhugh et al. (1950) fed rats diets containing mercury at 0, 0.5, 2.5, 10, 40 or 160 ppm from mercuric acetate. A minimum of 20 animals (10/sex) were included in each group. Two males and two females from each group were sacrificed after 1 year, the remainder after 2 years. Males, but not females, at 160 ppm appeared to have ~10% reduction in body weight compared with controls. Feeding levels of <160 ppm did not affect body weights; food consumption was unaffected. Kidneys were significantly heavier in animals fed 40 and 160 ppm mercuric acetate. Livers appeared heavier, but differences were not statistically significant.

Microscopic evaluation of the kidneys showed varying degrees of damage to the proximal convoluted tubules from hypertrophy and dilatation to the tubules becoming "small cysts" lined with "low non-descript epithelium". At later stages, cortical fibrosis was seen as well as atrophy and fibrosis of the glomeruli and other portions of the tubules, thought to be secondary to proximal tubule damage. Females appeared to be more severely affected than males. Treatment related changes were not seen at <40 ppm. At the end of 2 years, damage in the 40 ppm females was described as "slight to moderate," whereas controls were scored as "slight." Males at this dose level were said to have "slight damage", while controls were scored as "very slight."

3.2.1.2. ALKYL MERCURY -- The CNS appears to be the primary target of methylmercury intoxication. In man, primary lesions include destruction of cortical neurons especially in the areas of the occipital lobe concerned with vision, along with damage to the granular layer of the cortex. Clinical symptoms also suggest damage to peripheral nerves, but histopathological documentation is lacking. Clinical symptoms include paraesthesia, loss of sensation in the extremities and around the mouth, ataxia, constriction of the visual field and hearing impairment (WHO, 1976).

Human epidemiological data used for risk assessment have come primarily from two populations: Niigata, Japan, where poisoning resulted from eating contaminated fish and Iraq, where poisoning resulted from contaminated bread. In the Niigata outbreak, 17 patients were evaluated and in the Iraq outbreak, three separate studies were conducted, each looking at different populations. Briefly, Bakir et al. (1973) reported on 120 patients; Mufti et al. (1976) surveyed 936 persons from high exposure areas; and Shahristani et al. (1976) reported on 184 individuals. WHO (1976) and U.S. EPA (1980b) provide complete descriptions of these studies, as well as descriptions of other epidemiological studies that have not been used for risk assessment.

In the evaluation of these epidemiological data, two problems critical to risk assessment have been addressed. The first is the lowest blood levels of mercury (a reflection of cumulative body burden) associated with adverse effects and the second is the relationship of mercury ingestion to blood level (i.e., what exposure level is associated with the critical blood Hg level).

A Swedish Expert Group (1971) reported two methods that employed the Niiagata data to estimate blood levels of mercury associated with onset of symptoms. The estimate that was adopted in their estimate of acceptable daily exposure levels was reported by Berglund et al. (1971). They calculated the relationship between the measured blood mercury levels and the time that symptoms were first reported to occur. From this, they back-calculated to estimate what blood mercury levels would have been at the time of symptom onset. This level was estimated to be $\geq$0.2 μg Hg/g blood. Tsubaki et al. (1978) subsequently re-examined hair samples from this population for Hg levels. Their data indicate that there may have been problems with the original analytical technique and that the critical blood Hg estimate should probably have been closer to 0.3 μg Hg/g blood.

Other estimates of critical blood Hg levels have used the Iraqi data. Clarkson et al. (1976) estimated that blood mercury levels in the population reported by Bakir et al. (1973) associated with a paraesthetic incidence above background were 480 ng/mℓ. Shahristani et al. (1976) used hair mercury levels to estimate blood levels associated with signs of intoxication and estimated 480 ng Hg/mℓ blood as the threshold level. WHO (1976) estimated blood levels of 500 ng/mℓ to be threshold for symptoms of toxicity. Their estimates were based on estimated mercury ingestion from bread.

In summary, the lowest blood mercury level reported as an estimated threshold for neurological effects is 200 ng Hg/g blood. Other studies have not supported symptoms at such low levels. The U.S. EPA (1980b) points out, however, that evidence from the Iraqi population is just emerging which suggests that perinatal effects may occur at blood Hg levels that do not cause clinical symptoms of poisoning in the mothers. In addition, subsequent follow-up of the Niiagata population has indicated delayed cases of mercury poisoning (U.S. EPA, 1980b). For these reasons, U.S. EPA (1980b) used the critical blood Hg value of 200 ng/mℓ as a basis for their criterion development.

Regarding the problem of estimating the exposure level associated with a given blood mercury level, the approach of the Swedish Expert Group (1971) will be discussed first. Their estimate was based on estimates published by Berglund et al. (1971). Berglund compiled data on consumption of mercury-contaminated fish and blood mercury levels for 227 people in Sweden and Finland. Based on these relationships, it was estimated that a daily intake of 0.3 μg/day would result in a blood mercury concentration of 0.2 μg/g.

Several other relationships that differ slightly from this have been developed (WHO, 1976). The other estimate is that of Miettinen (1973), which was the estimate used to establish suggested maximum intake levels by both WHO (1976) and U.S. EPA (1980b). It was chosen because it is the most conservative estimate. Miettinen (1973) estimated the relationship between ingested mercury and blood levels from radioactive tracer studies of methylmercury administered to volunteers. In this study, a one:one relationship was established (i.e., 1 ng Hg/mℓ blood = a daily average intake of 1 μg/day).

Nordberg and Strangert (1976) have mathematically modeled risk of paraesthesia related to ingestion of various amounts of methylmercury. They used data on absorpton, distribution and half-life of methylmercury in conjunction with data relating blood mercury levels to threshold for paraesthesia. A major difference between their model and previous extrapolations is that they incorporated information on individual variation in biological half-life rather than using a fixed value. Dose-response curves developed from their model are shown in Figure 3-1. Using this model, they estimated that the risk of poisoning following long-term consumption of 0.3 mg Hg/70 kg, the acceptable intake level developed by Swedish Expert Group, was 0.02%.

3.2.2. Inhalation.

3.2.2.1. INORGANIC MERCURY -- Classical symptoms of mercury vapor intoxication (mental disturbances, objective tremors and gingivitis) have been observed following chronic occupational exposure to average air concentrations >0.1-0.2 mg Hg/m³ (Neal et al., 1937, 1941; Bidstrup et al., 1951; Friberg, 1951; Rentos and Seligman, 1968). Smith et al. (1970), in a comparative study of >500 workers exposed to mercury in chloralkali plants, reported an increase in frequency of nonspecific symptoms (loss of appetite, weight loss and shyness) in workers exposed to 0.06-0.1 mg Hg/m³. Objective tremors were observed at higher concentrations >0.1 mg Hg/m³.

Exposure to 0.25-1.0 mg Hg/m³ in a felt hat factory resulted in symptoms of mercury toxicity in 67% of the female workers (Kesic and Haeusler, 1951). Neal et al. (1937, 1941) studied workers in the felt hat industry where application of mercuric nitrate to rabbit fur resulted in the release of mercury vapor, volatile mercury compounds, and dust contaminated with mercury compounds. Of workers exposed to an air concentration of 0.24 mg Hg/m³ for 20 years, 54% had observable tremors. Exposure to 0.1 mg

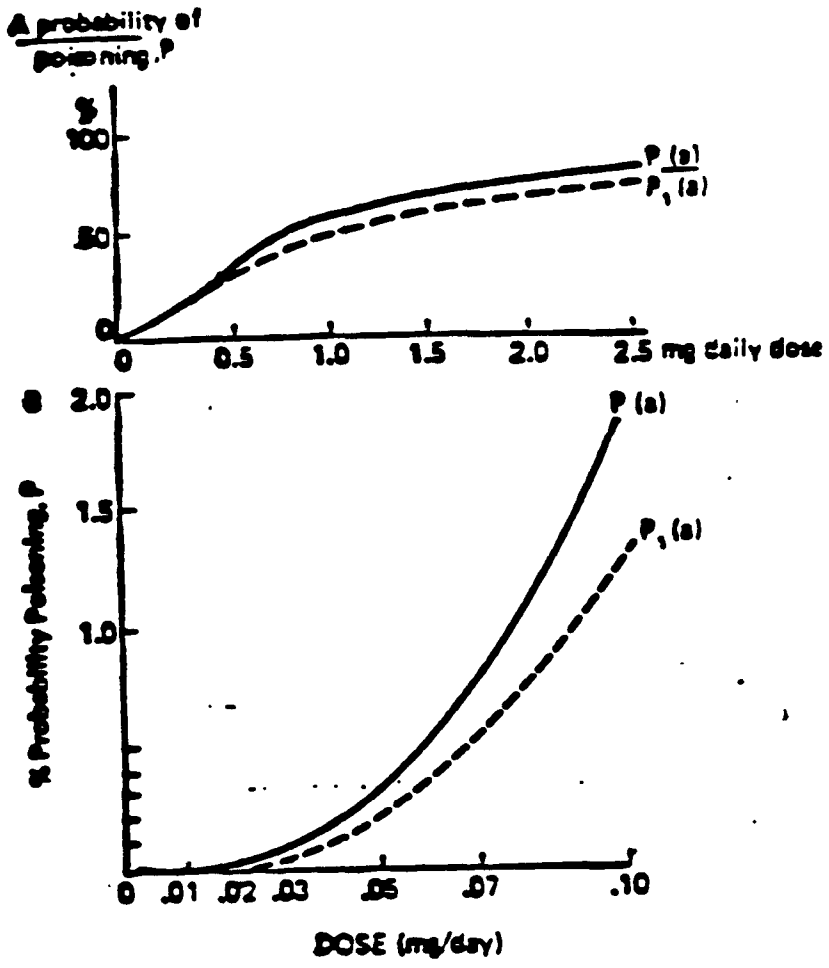

FIGURE 3-1

Dose-related curve for long-term exposure to methylmercuric compounds in human beings (50 kg bw). A = whole dose-response curve; B = detailed presentation of the curve representing lower doses; a = daily dose of Hg in the form of $MeHg^+$; $P_1(a)$ = probability of poisoning calculated for the total population; P(a) = probability of poisoning for the part of the population with biological half-time of 64 days. Probability P=1.0 corresponds to 100%.

Source: Nordberg and Strangert, 1976

Hg/m³ for 20 years resulted in symptoms "not grave enough to warrant diagnosis of mercury poisoning" in 10% of the exposed workers. Baldi et al. (1953) reported no cases of mercury poisoning at exposure levels <0.1 mg/m³. In contrast, Bidstrup et al. (1951) and Turrian et al. (1956) have reported psychological disturbances following exposure to concentrations of mercury <0.1 mg/m³. After a thorough review of the literature, WHO (1976) concluded that "it is impossible at this time to establish a lower exposure limit at which no effects occur."

Rentos and Seligman (1968) reported symptoms of mercury poisoning in 9/13 workers exposed to concentrations from 0.08-0.68 mg Hg/m³. They reported no symptoms in 9 workers exposed to average concentrations of 0.02 mg/m³. These data, although extremely limited, suggest that a NOAEL may fall somewhere between 0.02 and 0.1 mg Hg/m³.

3.2.2.2. ALKYL MERCURY -- There are few data concerning inhalation exposure to alkyl mercury compounds. ACGIH (1980) cited two primary pieces of evidence in support of a TLV: a suggested limit of 0.01 mg/m³ based on Swedish industrial experience and an occupational study where consistent symptoms of poisoning were not seen following exposure to concentrations between 0.01 and 0.1 mg Hg/m³.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral.

3.3.1.1. INORGANIC MERCURY -- Pertinent data regarding teratogenicity due to orally administered inorganic mercury could not be located in the available literature.

3.3.1.2. ALKYL MERCURY -- Several investigators have reported embryotoxic and teratogenic effects in experimental animals treated with methylmercury (Oharazawa, 1968; Fujita, 1969; Matsumoto et al., 1967; Nonaka, 1969; Morikawa, 1961; Spyker and Smithberg, 1972; Olson and Massaro, 1977).

The most common findings are neurological effects, but Oharazawa (1968) reported an increased frequency of cleft palate in mice. Reduced birth rates and possible neurological damage have been reported at doses of 0.1 mg Hg/kg bw/day (Fujita, 1969).

Brain damage, but not anatomical defects, have been reported in humans exposed prenatally to methylmercury (see Section 3.1.1.2.). These epidemiological studies may not have been sensitive enough to detect possible teratogenic effects of methylmercury in human populations.

3.3.2. Inhalation.

3.3.2.1. INORGANIC MERCURY -- Baranski and Szymczyk (1973) exposed female rats to high concentrations (LC_{25}) of mercury vapors either before breeding or during gestation. No effects were observed on histopathology, birth weights or teratology; however, large percentages of the pups died by postnatal day 6.

3.3.2.2. ALKYL MERCURY -- Pertinent data regarding the teratogenicity or other reproductive effects of inhaled methylmercury could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Dietary selenium intake is known to be a modifying factor in mercury toxicity. Increased selenium intake has been observed to counteract the toxicity of both organic and inorganic compounds (Underwood, 1977). Kosta et al. (1975) found that mercury mine workers accumulated mercury and selenium in their tissues in approximately a 1:1 molar ratio, thus tolerating high mercury levels with no apparent ill effects.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic potential of mercury in humans could not be located in the available literature.

4.2. BIOASSAYS

Pertinent data regarding the carcinogenic potential of mercury in experimental animals could not be located in the available literature. Mercuric chloride is being tested for carcinogenicity by the National Toxicology Program, but the results of this study are not yet available (NCI, 1983).

4.3. OTHER RELEVANT DATA

4.3.1. Inorganic Mercury. Pertinent data regarding the mutagenicity of metallic mercury could not be located in the available literature.

4.3.2. Alkyl Mercury. Methylmercury has been observed to block mitosis in plant cells, human leukocytes treated *in vivo* and human cells treated *in vitro*; to induce chromosome breaks in plant cells; and to induce point mutations in *Drosophila* (Ramel, 1972; Swedish Expert Group, 1971). Skerfving et al. (1974) found a positive correlation between blood concentrations of methylmercury and the frequency of chromosome breaks in 23 Swedish subjects who consumed diets high in fish products.

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the risk to humans associated with oral or inhalation exposure to mercury. No data are available regarding the carcinogenic potential of mercury in humans or animals. Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), mercury is most appropriately designated a Group D - Not classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

Drinking water standards of 1 and 2 μg Hg/ℓ have been recommended by WHO (1971) and U.S. EPA (1973), respectively. The U.S. EPA (1980b) has established an ambient water criterion of 144 ng/ℓ, which considers mercury consumed both in drinking water and in contaminated aquatic organisms. This is based on an estimated ADI of 20 μg/day.

The ACGIH (1980, 1983) has recommended a TLV of 0.05 mg/m³ and a STEL of 0.15 mg/m³ for mercury vapor, a TLV of 0.01 mg/m³ for alkyl mercury compounds and a TLV of 0.10 mg/m³ for inorganic and arylmercury compounds. NIOSH (1973), in developing a standard for occupational exposure to inorganic mercury, concluded that

> "occupational exposure to mercury shall be controlled so that workers are not exposed to inorganic mercury at a concentration greater than 0.05 mg/m³ as a time-weighted average exposure for an 8-hour workday."

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

U.S. EPA (1984) has suggested that exposures to mixed mercury compounds not exceed 30 μg/day by combined routes. This value agrees well with the sum of the inhalation and oral values presented below for alkyl mercury compounds. In any mixed exposure situation, toxicity considerations will primarily reflect the alkyl compounds because of their much greater absorption efficiency by the GI tract. The values presented below for inorganic mercury are applicable only when exposures are strictly limited to inorganic compounds.

6.1.1. Oral.

6.1.1.1. INORGANIC MERCURY -- Although no data specifically addressing subchronic exposure are available, one chronic study has been reported (Fitzhugh et al., 1950). Based on the estimated AIC of 140 μg/day (see Section 6.2.1.1.), it is suggested that this dose can also serve as an AIS.

6.1.1.2. ALKYL MERCURY -- Both a Swedish Expect Group (1971) and U.S. EPA (1980b) have estimated ADIs for methylmercury. Both groups used the data from the Niiagata, Japan outbreak of mercury poisonings, which estimated a threshold blood level of 200 ng Hg/mℓ blood for the development of neurological symptoms. To extrapolate the long-term oral dose required to reach this blood level, the Swedish group used the data of Berglund et al. (1971), which suggested an intake of Hg of 300 μg/day. Using a safety factor of 10, they suggested an interim ADI of 30 μg/day. The U.S. EPA (1980b) used the values suggested by Miettinen (1973), which are somewhat more conservative and provide an estimated intake of 200 μg Hg/day. After applying an uncertainty factor of 10, the estimated ADI was 20 μg Hg/day.

Following the more conservative approach suggested by U.S. EPA (1980b) and WHO (1976), an AIS of 20 μg/day is suggested. This value is applicable to alkyl mercury and mixed inorganic-alkyl exposures.

6.1.2. Inhalation.

6.1.2.1. INORGANIC MERCURY AND SALTS -- As discussed previously, dose response data are inadequate to define a "no-effect" exposure level for mercury vapor. The literature as a whole indicates that effects may occur at exposure levels of 0.1 mg Hg/m³. A small amount of data suggests that 0.02 mg Hg/m³ does not result in symptoms of toxicity. The TLV for mercury vapor, 0.05 mg/m³ (ACGIH, 1983), is bracketed by these values. In addition, Baranski and Szymczyk (1973) reported an increase in spontaneous abortions and mastopathy among woman exposed to maximum concentrations of 0.08 mg Hg/m³. Available data indicate that 0.005 mg/m³ should be protective for subchronic inhalation exposures to inorganic mercury and mercury vapor. This value is based on the TLV for mercury vapor divided by an uncertainty factor of 10. Although a separate TLV of 0.1 mg Hg/m³ has been suggested for inorganic mercury compounds (ACGIH, 1983), a single most conservative estimate is suggested for both mercury vapor and inorganic mercury compounds. Using an estimated breathing volume of 10 m³/workday and multiplying by 5/7 to correct for continuous exposure, the estimated acceptable exposure level of 0.005 mg Hg/m³ converts to an AIS of 35.7 μg/day.

6.1.2.2. METHYLMERCURY -- Although data directly addressing subchronic exposure to alkyl-mercury compounds by inhalation exposure are lacking, limited chronic occupational data are available. Based on these, ACGIH (1980) has suggested a TLV of 0.01 mg/m³. Incorporating an uncertainty factor of 10 to protect potentially more sensitive individuals in the

general population, assuming a workday breathing volume of 10 m^3, and multiplying by 5/7 results in an AIS of 7.14 µg/day.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral.

6.2.1.1. INORGANIC MERCURY -- Fitzhugh et al. (1950) reported morphological changes in kidney tissue in rats fed 40 ppm Hg (as mercuric acetate) in the diet for 2 years. Assuming that the data from the Fitzhugh et al. (1950) study are valid and that rats consume food equivalent to 5% of their body weight each day, this study establishes a LOAEL of 2 mg/kg/day. Applying uncertainty factors of 10 to convert from a LOAEL to a NOAEL, 10 for interspecies conversion and 10 to allow for the most sensitive members of the population results in an AIC of 2 µg/kg bw/day or 140 µg/day for a 70 kg human. This value is applicable only in situations where exposure to alkyl mercury is ruled out.

6.2.1.2. METHYLMERCURY -- An interim ADI of 20 µg/day for alkyl mercury or mixed alkyl-inorganic exposure is suggested. See Section 6.1.1.2. for the rationale.

The oral toxicity of alkyl mercury compounds was reviewed and an RQ was derived based on the occurrence of retarded psychomotor development in children whose mothers consumed methylmercury while pregnant. Marsh et al. (1977) correlated these effects with levels of mercury in mothers' hair ranging from 99-384 µg/g. These symptoms were present, but far less common in infants whose mothers' hair contained <85 µg/g. Although exposure data were not provided, the data of Marsh et al. (1977) indicate that exposure during gestation resulting in maternal hair levels of <85 µg/g may be near the threshold for psychomotor retardation in infants. Since 85 µg/g is near the median of the range (50-125 µg/g) that the WHO (1976)

correlated with a long-term intake of methylmercury of 3-7 μg/kg bw/day, it seems reasonable to suggest that an intake of methylmercury of 3 μg/kg bw/day may approximate the MED for the syndrome in infants. This MED corresponds to 210 μg/day for a 70 kg human, which can also be expressed as 0.2 mg/day. Multiplying by the ratio of the formula weight of mercury to methylmercury results in an MED for mercury from alkyl mercury of 0.18 mg/day, which corresponds to an RV_d of 6.6. The signs observed, a low incidence of neurologic dynsfunction, are assigned an RV_e of 9. A CS of 59.4, the product of RV_d and RV_e, is calculated.

6.2.2. Inhalation.

6.2.2.1. INORGANIC MERCURY -- Since the data used for the development of the inhalation AIS are primarily chronic, the approach used in Section 6.1.2.1 also will be used here. The calculated inhalation AIS was 35.7 μg/day for mercury vapor and inorganic mercury salts. For chronic exposures, an additional uncertainty factor of 10 is added to protect the potentially most sensitive segments of the general population. This results in a suggested AIC of 3.6 μg/day. This may be an overly conservative estimate, and should be re-evaluated when more data are available at the lower end of the dose-response curve.

RQ documents have been prepared for several inorganic compounds of mercury (mercuric nitrate: U.S. EPA, 1983b; mercuric thiocyanate: U.S. EPA, 1983c; mercurous nitrate: U.S. EPA, 1983d; mercuric sulfate: U.S. EPA, 1983e; mercury fulminate: U.S. EPA, 1983f). Data sufficient for deriving an RQ were available only for mercuric nitrate. U.S. EPA (1983b) calculated a CS for the CNS effects (tremors) observed by Neal et al. (1937, 1941) in workers occupationally exposed to mercury in the air at 0.24 mg/m³, resulting from the applications of mercuric nitrate to rabbit fur in the

manufacture of felt hats. This concentration is equivalent to 0.39 mg mercuric nitrate/m³ of air obtained by multiplying 0.24 mg Hg/m³ by the ratio of the formula weight of mercuric nitrate ($Hg(NO_3)_2$:324.6 mg/mmol) to that of mercury (Hg:200.6 mg/mmol). Assuming that occupational exposure results in the inhalation of 10 m³ of air/day for 5 days/week, and applying an assumed absorption factor of 0.5, a human dose (MED) of 1.39 mg/day for mercuric nitrate was obtained. This MED corresponds to an RV_d of 5.3. The CNS effects observed were assigned an RV_e of 8. A CS of 42.4 is obtained as the product of RV_d and RV_e.

6.2.2.2. METHYLMERCURY -- An AIC of 7.14 µg/day can be calculated for alkyl mercury compounds based on the TLV of 0.01 mg/m³ (see Section 6.1.2.2.).

6.3. CARCINOGENIC POTENCY (q_1*)

None of the available data indicate a carcinogenic potential for either inorganic mercury or methylmercury following either oral or inhalation exposure. Therefore, no q_1* has been calculated.

7. REFERENCES

Aberg, B., L. Ekman, R. Falk, U. Greitz, G. Persson and J-O. Snihs. 1969. Metabolism of methyl mercury (^{203}Hg) compounds in man. Excretion and distribution. Arch. Environ. Health. 19: 478-484. (Cited in U.S. EPA, 1980b)

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air. Fourth edition with supplements through 1982. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984. Cincinnati, OH.

Amin-Zaki, L., S. Elhassani, M.A. Majeed, T.W. Clarkson, R.A. Doherty and M. Greenwood. 1974a. Intrauterine methylmercury poisoning in Iraq. Pediatrics. 54(5): 587-595. (Cited in U.S. EPA, 1980b)

Amin-Zaki, L., M.A. Majeed, T.W. Clarkson, R.A. Doherty and M.R. Greenwood. 1974b. Studies of infants postnatally exposed to methylmercury. J. Pediatr. 85: 81-84. (Cited in U.S. EPA, 1980b)

Bakir, F., et al. 1973. Methylmercury poisoning in Iraq. Science. 181: 230-241. (Cited in U.S. EPA, 1980b)

Baldi, G., E.C. Vigliani and N. Zurlo. 1953. Chronic mercurialism in felt hat industries. Med. Lav. 44: 161-168. (Cited in NIOSH, 1973; U.S. EPA, 1983b)

Baranski, B. and I. Szymczyk. 1973. Effects of mercury vapors upon reproductive function of the female white rat. Med. Pracy. 24(3): 249-261. (Cited in U.S. EPA, 1980b)

Berglund, F., M. Berein, G. Berke, et al. 1971. Methylmercury in fish, a toxicologic-epidemiologic evaluation of risks, report from an expert group. Nord. Hyg. T. Suppl.4.

Berlin, M.H., G.F. Nordberg and F. Serenius. 1969. On the site and mechanism of mercury vapor resorption in the lung. Arch. Environ. Health. 18: 42-50. (Cited in U.S. EPA, 1980b)

Bidstrup, P.L., J.A. Bonnell, D.G. Harvey and S. Locket. 1951. Chronic mercury poisoning in men repairing direct-current meters. Lancet. 251: 856-860. (Cited in U.S. EPA, 1980b)

Bornmann, G., G. Henke, H. Alfes and H. Möllmann. 1970. Ober die enterale Resorption von metallischem Quecksilber. Arch. Toxikol. 26: 203-209. (Ger.) (Cited in U.S. EPA, 1980b)

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-related Environmental Fate of 129 Priority Pollutants, Vol. I. U.S. EPA, Office of Water Planning and Standards, Office of Water and Waste Management, Washington, DC. EPA 440/4-79-029a.

Choi, B.H., L.W. Lapham, L. Amin-Zaki and T. Saleem. 1977. Abnormal neuronal migration in human fetal brain due to mercury poisoning. Am. J. Pathol. 84: 55A. (Cited in U.S. EPA, 1980b)

Clarkson, T.W. 1971. Epidemiological and experimental aspects of lead and mercury contamination of food. Food Cosmet. Toxicol. 9: 229-243. (Cited in U.S. EPA, 1980b)

Clarkson, T.W. 1977. Plenary lecture -- Mercury poisoning. In: Clinical Chemistry and Chemical Toxicology of Metals, S.S. Brown, Ed. Elsevier/North Holland, Amsterdam. p. 189-200. (Cited in U.S. EPA, 1980b)

Clarkson, T.W., et al. 1976. An outbreak of methylmercury poisoning due to consumption of contaminated grain. Fed. Proc. 35: 2395-2399. (Cited in U.S. EPA, 1980b)

Derobert, L. and S. Tara. 1950. Mercury intoxication in pregnant women. Ann. Med. Legale, Paris. 30: 4. (Cited in U.S. EPA, 1980b)

Edwards, G.N. 1865. Two cases of poisoning by mercuric methide. St. Bart's Hospital Rep. 1: 141. (Cited in U.S. EPA, 1980b)

Engleson, G. and T. Herner. 1952. Alkyl mercury poisoning. Acta Pediat. Scan. 41: 289-293. (Cited in U.S. EPA, 1980b)

Evans, H.L., R.H. Garman and B. Weiss. 1977. Methylmercury: Exposure duration and regional distribution as determinants of neurotoxicity in nonhuman primates. Toxicol. Appl. Pharmacol. 41: 15-33. (Cited in U.S. EPA, 1980b)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. Federal Register 49:46294-46299.

Fitzhugh, O.G., A.A. Nelson, E.P. Laug and F.M. Kunze. 1950. Chronic oral toxicities of mercuri-phenyl and mercuric salts. Arch. Ind. Hyg. Occup. Med. 2: 433-441.

Friberg, L. 1951. Aspects of chronic poisoning with inorganic mercury based on observed cases. Nord. Hyg. Tidskr. 32: 240-249. (Cited in U.S. EPA, 1980b)

Friberg, L. and G. Nordberg. 1973. Inorganic mercury -- A toxicological and epidemiological appraisal. In: Mercury, Mercurials and Mercaptans, M.W. Miller and T.W. Clarkson, Ed. Charles C. Thomas, Springfield, IL. p. 5-22. (Cited in U.S. EPA, 1980b)

Friberg, L. and J. Vostal, Ed. 1972. Mercury in the Environment. Chemical Rubber Co., Cleveland, OH. (Cited in U.S. EPA, 1980b)

Fujita, E. 1969. Experimental studies on organic mercury poisoning: The behavior of Minamata disease causal agent in maternal bodies and its transfer to their infants via either placenta or breast milk. J. Kumanoro Med. Soc. 43: 47-63. (Cited in U.S. EPA, 1980b)

Gleason, M.N., et al. 1957. In: Clinical Toxicology of Commercial Products. Williams and Wilkins Co., Baltimore, MD. p. 154. (Cited in U.S. EPA, 1980b)

Harada, Y.C. 1968. Clinical investigations on Minamata disease. C. Congenital (or fetal) Minamata disease. In: Minamata Disease, Study Group of Minamata Disease, M. Kutsuna, Ed. Kumomoto University, Japan. (Cited in U.S. EPA, 1980b)

Hunter, D. and D.S. Russell. 1954. Focal cerebral and cerebellar atrophy in a human subject due to organic mercury compounds. J. Neurol. Neurosurg. Psychiat. 17: 235-241. (Cited in U.S. EPA, 1980b)

Hunter, D., R.R. Bomford and D.S. Russell. 1940. Poisoning by methyl mercury compounds. Quart. J. Med. 33: 193-213. (Cited in U.S. EPA, 1980b)

Hurch, J.B., et al. 1976. Clearance of mercury (^{197}Hg, ^{203}Hg) vapor inhaled by human subjects. Arch. Environ. Health. 4: 302. (Cited in U.S. EPA, 1980b)

Katsuna, M., Ed. 1968. Minamata Disease. Kumomata University, Japan. (Cited in U.S. EPA, 1980b)

Katsuniko, M. and G. Takumi. 1976. Mercury in the air and precipitation. Geochem. J. 10: 107. (Cited in U.S. EPA, 1980b)

Kesic, B. and V. Haeusler. 1951. Hematological investigation on workers exposed to mercury vapor. Ind. Med. Surg. 20: 485-488. (Cited in U.S. EPA, 1983b)

Kosta, L., A.R. Byrne and V. Zelenko. 1975. No title provided. Nature (London). 254: 238. (Cited in Underwood, 1977)

Kostial, K., D. Kello, S. Jugo, I. Rabar and T. Maljkovic. 1978. Influence of age on metal metabolism and toxicity. Environ. Health Perspect. 25: 81-86. (Cited in U.S. EPA, 1980b)

Marsh, D.O., et al. 1977. Fetal methylmercury poisoning: New data on clinical and toxicological aspects. Trans. Am. Neurol. Assoc. 102: 69-71. (Cited in U.S. EPA, 1980b)

Matsumoto, H., A. Suzuki, C. Morita, K. Nakamura and S. Saeki. 1967. Preventive effect of penicillamine on the brain defect of fetal rat poisoned transplacentally with methyl mercury. Life Sci. 6: 2221-2226.

Miettinen, J.K. 1973. Absorption and elimination of dietary mercury (Hg^{2+}) and methylmercury in man. In: Mercury, Mercurials and Mercaptans, M.W. Miller and T.W. Clarkson, Ed. Charles C. Thomas, Springfield, IL. p. 233-243. (Cited in U.S. EPA, 1980b)

Milne, J., A. Christophers and P. De Silva. 1970. Acute mercurial pneumonitis. Br. J. Ind. Med. 27: 334-338. (Cited in U.S. EPA, 1980b)

Morikawa, N. 1961. Pathological studies on organic mercury poisoning. I. Experimental organic mercury poisoning in cats and its relation to the causative agent of Minamata disease. Kumamoto Med. J. 14: 71-83. (Cited in U.S. EPA, 1980b)

Morrow, P.E., F.R. Gibb and L. Johnson. 1964. Clearance of insoluble dust from the lower respiratory tract. Health Phys. 10: 543-555. (Cited in U.S. EPA, 1980b)

Mufti, A.W., et al. 1976. Epidemiology of organo-mercury poisoning in Iraq. I. Incidence in a defined area and relationship to the eating of contaminated bread. In: WHO Conference on Intoxication Due to Alkyl Mercury-treated Seed, November 9-13, 1974, Baghdad, Iraq. Suppl. to WHO Bull. 53, Geneva. p. 23-36. (Cited in U.S. EPA, 1980b)

NAS (National Academy of Sciences). 1978. An assessment of mercury in the environment. Panel on Mercury. Washington, DC. (Cited in U.S. EPA, 1980b)

NCI (National Cancer Institute). 1983. National Toxicology Program Toxicology Research and Testing Program. Management Status Report, December 5.

Neal, P., R.R. Jones, J.J. Bloomfield, J.M. Dalla Valle and T.I. Edwards. 1937. A Study of Chronic Mercurialism in the Hatters Furcutting Industry. Publ. Health Bull. 234. PHS, U.S. Treasury Dept. (Cited in U.S. EPA, 1983b; NIOSH, 1973)

Neal, P., R.H. Flinn, T.I. Edwards and W.H. Reinhart. 1941. Mercurialism and Its Control in the Felt Hat Industry. PHS, Publ. Health Bull. 263. (Cited in U.S. EPA, 1983b; NIOSH, 1973)

Nielsen-Kudsk, F. 1965. Absorption of mercury vapor from the respiratory tract in man. Acta Pharmacol. 23: 250. (Cited in U.S. EPA, 1980b)

NIOSH (National Institute for Occupational Safety and Health). 1973. Criteria for a Recommended Standard...Occupational Exposure to Inorganic Mercury. U.S. DHEW, PHS, CDC, Rockville, MD. Publ. No. 222-223. (Cited in U.S. EPA, 1983b)

Nonaka, I. 1969. An electron microscopical study on the experimental congenital Minamata disease in rat. Kumamoto Med. J. 22: 27-33. (Cited in U.S. EPA, 1980b)

Nordberg, G.F., Ed. 1976. Effects and Dose-Response of Toxic Metals. Elsevier, Amsterdam. (Cited in U.S. EPA, 1980b)

Nordberg, G.F. and P. Strangert. 1976. Estimations of a dose-response curve for long-term exposure to methylmercuric compounds in human beings taking into account variability of critical organ concentration and biological half-time: A preliminary communication. In: Effects and Dose-Response Relationships of Toxic Metals, Report presented to International Meeting Arranged by the Subcommittee on the Toxic Metals, Tokyo, G.F. Nordberg, Ed. Elsevier, Amsterdam. p. 18. (Cited in U.S. EPA, 1980b)

Oharazawa, H. 1968. Chromosomal abnormalities and teratogenesis induced by ethyl mercuric phosphate in pregnant mice. Nippon Sanka-Fujinka Gakk: Zasshi. 20: 1479. (Cited in U.S. EPA, 1980b)

Olson, F.C. and E.J. Massaro. 1977. Pharmacodynamics of methyl mercury in the murine maternal/embryo:fetal unit. Toxicol. Appl. Pharmacol. 39: 263-273. (Cited in U.S. EPA, 1980b)

Pierce, P.E., et al. 1972. Alkyl mercury poisoning in humans. Report of an outbreak. J. Am. Med. Assoc. 220: 1439-1442. (Cited in U.S. EPA, 1980b)

Piotrowski, J., et al. 1973. Further investigations on binding and release of mercury in the rat. In: Mercury, Mercurials and Mercaptans, M.W. Miller and T.W. Clarkson, Ed. Charles C. Thomas, Springfield, IL. p. 247. (Cited in U.S. EPA, 1980b)

Rahola, T., et al. 1971. The biological half-time of inorganic mercury (Hg^{2+}) in man. Scand. J. Clin. Invest. Abstr. 27: 77 (Suppl. 116). (Cited in U.S. EPA, 1980b)

Ramel, C. 1972. Genetic effects. In: Mercury in the Environment -- A Toxicological and Epidemiological Appraisal, L. Friberg and J. Vostal, Ed. Chemical Rubber Co., Cleveland, OH. p. 169-181. (Cited in U.S. EPA, 1980b)

Rentos, P. and E. Seligman. 1968. Relationship between environmental exposure to mercury and clinical observation. Arch. Environ. Health. 16: 794-800. (Cited in U.S. EPA, 1980b)

Shahristani, H., et al. 1976. Mercury in the hair as an indicator of total body burden. In: WHO Conference on Intoxication Due to Alkyl Mercury Treated Seed, November 9-13, 1974, Baghdad, Iraq. Suppl. to WHO Bull. 53, Geneva. (Cited in U.S. EPA, 1980b)

Skerfving, S., K. Hansson, C. Mangs, J. Lindsten and N. Ryman. 1974. Methylmercury induced chromosome damage in man. Environ. Res. 7: 83-112. (Cited in U.S. EPA, 1980b)

Smith, R.G., A.J. Vorwald, L.S. Patil and T.F. Mooney, Jr. 1970. Effects of exposure to mercury in the manufacture of chlorine. Am. Ind. Hyg. Assoc. J. 31: 687-700. (Cited in U.S. EPA, 1980b)

Snyder, R.D. 1971. Congenital mercury poisoning. New Engl. J. Med. 284: 1014-1016. (Cited in U.S. EPA, 1980b)

Spyker, J.M. and M. Smithberg. 1972. Effects of methylmercury on prenatal development in mice. Teratology. 5: 181-190. (Cited in U.S. EPA, 1980b)

Suzuki, T. and A. Tonaka. 1971. Methylmercury in maternal and fetal red blood cells. Ind. Med. 13: 52. (Cited in U.S. EPA, 1980b)

Swedish Expert Group. 1971. Methylmercury in fish -- Toxicological epidemiological evaluation of risks. Report from an expert group. Nordisk. Hyg. Tidsknift. Suppl. 4. (Cited in U.S. EPA, 1980b)

Takeuchi, T., Ed. 1968. Minimata Disease. Study Group of Minimata Disease. Kumamoto University Press. p. 141. (Cited in U.S. EPA, 1980b)

Teisinger, J. and V. Fiserova-Bergerova. 1965. Pulmonary retention and excretion of mercury vapors in man. Ind. Med. Surg. 34: 580-584. (Cited in U.S. EPA, 1980b)

Tsubaki, T. and K. Irukayama. 1977. Minamata Disease. Elsevier Publ. Co., Amsterdam. (Cited in U.S. EPA, 1980b)

Tsubaki, T., et al. 1978. Clinical, epidemiological and toxicological studies on methylmercury poisoning. In: Proc. First Int. Cong. on Toxicol., Toronto, Canada, November. p. 339-357. (Cited in U.S. EPA, 1980b)

Turner, M.D., et al. 1974. Methylmercury (MeHg) in human population eating large quantities of marine fish in Northern Peru. In: Proc. First Int. Cong. Mercury, Barcelona, May 5-10. (Cited in U.S. EPA, 1980b)

Turner, M.D., et al. 1975. Studies on volunteers consuming methylmercury in tuna fish. Clin. Res. 23: 2. (Cited in U.S. EPA, 1980b)

Turrian, H., E. Grandjean and V. Turrian. 1956. Industrial hygiene and medical studies in mercury plants. Schweiz Med Wochenschr. 86: 1091-1094 (Ger.) (Cited in NIOSH, 1973).

Underwood, E.J. 1977. Trace Elements in Human and Animal Nutrition, 4th ed. Academic Press, NY.

U.S. EPA. 1973. Water Quality Criteria, 1972. Ecol. Res. Ser. Rep. Comm. of Water Quality Criteria. NAS, U.S. GPO, Washington, DC. EPA R3/73/033. (Cited in U.S. EPA, 1980b)

U.S. EPA. 1980a. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45: 79347-79357.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Mercury. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-058. NTIS PB 81-117699.

U.S. EPA. 1983a. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity for Mercuric Nitrate. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983c. Reportable Quanitity for Mercuric Thiocyanate. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983d. Reportable Quanitity for Mercurous Nitrate. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983e. Reportable Quanitity for Mercuric Sulfate. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983f. Reportable Quanitity for Mercury Fulminate. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Mercury Health Effects Update. Health Issue Assessment. Final Report. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-84-019F. NTIS PB 85-123925.

U.S. EPA Task Group on Metal Accumulation. 1973. Accumulation of toxic metals with special reference to their absorption, excretion and biological half-times. Environ. Phys. Biochem. 3: 65-107. (Cited in U.S. EPA, 1980b)

Weast, R.C., Ed. 1980. CRC Handbook of Chemistry and Physics. CRC Press, Inc., Boca Raton, FL. p. B119-B120.

WHO (World Health Organization). 1971. International Standards for Drinking Water, 3rd ed. Geneva. (Cited in U.S. EPA, 1980b)

WHO (World Health Organization). 1976. Environmental Health Criteria, Mercury. Geneva. (Cited in U.S. EPA, 1980b)

Zepp, R.G., N.L. Wolfe and J.A. Gordon. 1973. Photodecomposition of phenylmercury compounds in sunlight. Chemosphere. 3: 93-99.

APPENDIX A

Summary Table for Inorganic Mercury
(assumes no exposure to alkyl compounds)

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	human	TLV 0.05 mg/m³	abortion, mastopathy	35.7 µg/day	ACGIH, 1983
AIC	human	TLV 0.05 mg/m³	neurological changes	3.6 µg/day	ACGIH, 1983
Maximum composite score	human	0.39 mg $Hg(NO_3)_2$ m³ occupational (RV_d = 5.3)	CNS signs (tremors) (RV_e = 8)	42.4	Neal et al., 1937, 1941; U.S. EPA, 1983b
Oral					
AIS	rat	40 mg Hg/kg diet	altered kidney morphology	140 µg/day	Fitzhugh et al., 1950
AIC	rat	40 mg Hg/kg diet	altered kidney morphology	140 µg/day	Fitzhugh et al., 1950

ND = Not derived