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Summary Review of Health Effects Associated with Mercuric Chloride:

Health Issue Assessment

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
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PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a source document for use by the Office of Air Quality Planning and Standards to support their information needs on the health effects of mercuric chloride, which is listed as a hazardous air pollutant in the Clean Air Act Amendments of 1990.

In the development of this assessment document, the scientific literature through August 1993 has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. Although the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in some instances on assumption rather than specific data. Appropriate information regarding sources, emissions, and ambient air concentrations is needed to provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

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1. SUMMARY AND CONCLUSIONS

Mercuric chloride ($HgCl_2$) is one of the more important inorganic mercury (Hg) compounds. A white crystal or powder at room temperature, $HgCl_2$ has been widely used in medicine, agriculture, and chemistry. Although most agricultural and pharmaceutical uses of mercury compounds have been discontinued in the United States in recent years, $HgCl_2$ is still used as a disinfectant or pesticide. It is also a useful catalyst or reagent in various chemical reactions.

The chemistry of $HgCl_2$ must be considered in the context of mercury chemistry in general, as the various species of mercury (Hg^0, Hg^{2+}, Hg_2^{2+}, and organic mercury) are interchangeable in environmental or biological situations. In other words, mercury entering an environmental system in one form (e.g., Hg^{2+} in $HgCl_2$) may be changed, in that system, into a different form (e.g., CH_3HgCl) with a different level or type of toxicity. A significant feature of mercury chemistry in general (including $HgCl_2$) is the strong affinity of mercury for sulfur and sulfhydryl groups. The binding or complexing of mercury to sulfhydryl groups of enzymes and other proteins is of central importance in many of the biochemical effects of mercury compounds.

Specific figures for the production, use, and emission of $HgCl_2$ are not available. Figures are available for total mercury use and emission by various types of industries in the United States, and, from the figures given for those industries that are known to use $HgCl_2$, an estimate of 138 metric tons was obtained for 1991 use of $HgCl_2$. Mercuric chloride may be released into the atmosphere from natural sources (e.g., geothermal activity) and anthropogenic sources (e.g., fossil fuel combustion, municipal waste incineration, or industries using $HgCl_2$). An estimate of 332 metric tons/year was obtained for combined Hg^0 and $HgCl_2$ atmospheric emissions in 1990 in the United States from anthropogenic sources.

Mercury, particularly elemental mercury vapors, can be transported great distances in the atmosphere and, when reentrainment is considered, has an effective residence time of up to 3 years. The major route of mercury removal from the atmosphere is probably rainfall.

Divalent mercury may be transformed into elemental or organic mercury in the air, water, and soil.

Total atmospheric mercury levels vary with the degree of industrialization and proximity to various natural and anthropogenic point sources. Estimated average background levels at 3,900 sites indicate that total atmospheric mercury is 1 to 2 ng Hg/m^3 in rural areas and 10 to 20 ng/m^3 in urban areas. Little specific information is available on the background concentration of $HgCl_2$ in the air, although $HgCl_2$ may account for 1 to 25% of the total atmospheric mercury, depending on the location.

Approximately 20,000 people in the United States are exposed to $HgCl_2$ through occupational use of the compound. The Occupational Safety and Health Administration (OSHA) recommends an exposure ceiling of 0.1 mg Hg/m^3 air for aryl and inorganic mercury, and the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a time-weighted average (TWA) exposure of 0.1 mg Hg/m^3 for aryl and inorganic mercury. Exposure of a working adult to 0.1 mg Hg/m^3 as $HgCl_2$ would mean a maximum inhalation of 1.35 mg $HgCl_2$/day (1.0 mg Hg/day), assuming a breathing rate of 10 m^3/work shift with 1 shift/day and no additional exposures. Assuming an average breathing rate of 20 m^3/day and a background level of 10 ng Hg/m^3 in an urban area, a nonoccupationally exposed adult could inhale 200 ng Hg/day, including up to 52 ng $HgCl_2$ (38 ng Hg or 19% of the total mercury). Exposure to mercury also occurs through inhalation of elemental mercury released from dental amalgam restorations and ingestion of inorganic mercury through corrosion of amalgam material into saliva (essentially, no mercury is absorbed following ingestion of elemental mercury). The estimated average intake of inorganic mercury (principally $HgCl_2$) for an adult from air, food, water, and dental amalgam restorations is between 3,900 and 24,600 ng Hg/day (3.9 to 24.6 μg Hg/day); the absorbed dose of inorganic mercury is between 300 and 2,500 ng Hg/day (0.3 to 2.5 μg Hg/day). Summaries of official standards for airborne mercury and estimated human intake of various forms of mercury are given in Tables 1-1 and 1-2, respectively. Other potential sources of nonoccupational human exposure to inorganic mercury compounds include skin ointments, surgical antiseptics, and accidental poisoning.

TABLE 1-1. SUMMARY OF OFFICIAL STANDARDS FOR AIRBORNE MERCURY

Standard		Source
Federal standard (OSHA)	0.10 mg Hg/m^3, ceiling[a], aryl and inorganic mercury	A
	0.01 mg Hg/m^3, TWA, organic mercury	A
	0.03 mg Hg/m^3, ceiling, STEL, alkyl mercury	A
ACGIH	0.05 mg Hg/m^3, TWA, mercury vapor, all forms except alkyl mercury	B
	0.01 mg Hg/m^3, TWA, alkyl mercury	B
	0.03 mg Hg/m^3, STEL, alkyl mercury	B
	0.10 mg Hg/m^3, TWA, aryl and inorganic mercury	B

[a]Given as 1 mg Hg/10 m^3 in the cited publication.

Abbreviations:
ACGIH = American Conference of Governmental Industrial Hygienists.
OSHA = Occupational Safety and Health Administration.
STEL = Short-term exposure limit (15 min).
TWA = Time-weighted average (8 h).

Sources:
A = Code of Federal Regulations (1992).
B = American Conference of Governmental Industrial Hygienists (1992).

Little specific information is available on the absorption of inhaled $HgCl_2$; the estimate generally used is 80%, although 40% absorption has been estimated in dogs. Less than 20% of ingested $HgCl_2$ is absorbed from the gastrointestinal tract, and 7% is the estimate used by both the U.S. Environmental Protection Agency (EPA) and the World Health Organization (WHO). Some $HgCl_2$ also may be absorbed through the skin, but the major route of human exposure to $HgCl_2$ is via the gastrointestinal tract.

The distribution of mercury compounds in the body and within organs is dependent on the dose and type of mercury received, the time elapsed since the dose was received, and the metabolic parameters of binding and reaction. Most divalent mercury is concentrated in the kidneys. Divalent mercury does not readily cross either the placental or blood-brain barriers, and relatively little mercury accumulates in the brain following exposure to divalent mercury as compared with exposure to elemental or organic mercury.

Total body burden of mercury has been estimated to be 13 mg, or 0.19 mg/kg (wet weight) for a 70-kg man. People from urban populations have been found to contain

TABLE 1-2. ESTIMATED AVERAGE DAILY INTAKE AND RETENTION (μg/day) OF ELEMENTAL MERCURY AND MERCURY COMPOUNDS IN THE GENERAL POPULATION NOT OCCUPATIONALLY EXPOSED TO MERCURY[a]

Exposure Source	Elemental Mercury Vapor	Inorganic Mercury Compounds	Methyl Mercury
Air[b,c]	0.03 (0.024)	0.002 (0.001)	0.008 (0.0064)
Food[b,c]			
Fish	0	0.6 to 0.94 (0.042 to 0.066)	0.32 to 2.4 (0.3 to 2.3)[e]
Nonfish	0	3.2 to 3.6 (0.22 to 0.25)[e]	0
Drinking water[b,c]	0	0.05 (0.0035)	0
Dental amalgams[b, d]	1.5 to 36 (1.2 to 29)	0 to 20 (0 to 1.4)	0
Total	1.5 to 36 (1.2 to 29)	3.9 to 24.6 (0.26 to 1.7)	0.33 to 2.4 (0.31 to 2.3)

[a]Values given are the estimated average daily intake; the figures in parentheses represent the estimated amount retained in the body of an adult. Values are quoted to two significant figures. Retention data are calculated assuming 80% absorption of all forms of inhaled mercury, 7% absorption of ingested inorganic mercury, and 90% absorption of ingested methyl mercury.

[b]Environmental Health Criteria 101: Methyl Mercury (World Health Organization, 1990).

[c]U.S. Environmental Protection Agency (1984a).

[d]Appendix II of U.S. Public Health Service Dental Amalgam Report (1992).

[e]Grant et al. (1991) estimate 3.2 μg/day total mercury intake in food with limited (average) fish consumption, 10 to 30% of which (0.32 to 0.96 μg/day) as methyl mercury. Therefore, the U.S. Environmental Protection Agency (1984a) estimates of 20 μg/day for inorganic mercury from nonfish food and 3.8 μg/day for methyl mercury from fish are considered high for the general population and are not included in the table.

statistically higher levels of mercury than people from rural populations. The normal upper limit for blood mercury levels is 10 to 30 μg Hg/L blood. The highest mercury concentrations in the body are generally found in the kidneys. Normal kidney levels of mercury are usually below 2.8 mg Hg/kg. The normal upper limit for mercury in urine is 25 to 30 μg Hg/L; urinary mercury levels are more closely related to blood levels than to kidney levels. The half-life of inorganic mercury in the human body is between 1 and 2 mo, although for certain organs, particularly the kidneys and brain, the retention times are somewhat longer. The major route of removal of inorganic mercury is via the urine, although the feces are also important.

Mercuric chloride is mutagenic in various experimental systems; however, cytotoxicity usually occurs at $HgCl_2$ levels sufficient to produce mutations or chromosome aberrations. Mercuric chloride does damage DNA, producing both single-strand breaks and DNA-DNA cross-links. Mercuric chloride inhibits spindle polymerization resulting in numerical chromosome aberrations (aneuploidy). No epidemiological studies are available that assess the potential carcinogenicity of $HgCl_2$. The only adequate carcinogenicity study of $HgCl_2$ is a 2-year study of rats and mice that were administered $HgCl_2$ by gavage. The forestomach of male rats exposed to 2.5 and 5 mg/kg/day, 5 days/week after 15 mo developed basal cell hyperplasia, which became extensive after 2 years. Focal papillary hyperplasia and squamous cell papillomas of the forestomach also were noted at 2 years. The National Toxicology Program (NTP) also reported an increased incidence of thyroid follicular cell adenomas and carcinomas in male rats, which may have been related to $HgCl_2$ exposure. Squamous cell papillomas also were observed in high-dose group female rats. The NTP reported "some evidence" of carcinogenic activity in male rats and "equivocal evidence of carcinogenic activity" in female rats related to administration of $HgCl_2$. The incidence of forestomach neoplasms in male and female mice were within the range of historical controls and could not be regarded as evidence of carcinogenic activity. However, NTP noted "equivocal evidence of carcinogenic activity" in male mice based on the occurrences of two renal tubule adenomas and one renal tubule adenocarcinoma. The EPA considered the relevant information for $HgCl_2$ and other mercuric salts and has assigned inorganic mercury a preliminary "C" classification, which means that inorganic mercury is considered a "possible human carcinogen". This classification is considered preliminary because it has not yet been posted

on the EPA Integrated Risk Information System (IRIS) database. The study of male rats provides the principal evidence for a carcinogenic effect from $HgCl_2$ exposure. However, high mortality in male rats from severe renal disease suggests that the potential toxicity of $HgCl_2$ may pose a greater hazard than its potential carcinogenicity.

Oral $HgCl_2$ exposures in the range of 1 to 4 mg/kg can affect various aspects of reproduction and development in experimental animals. Reported effects include delayed ovulation, decreased male fertility, and inhibited development of embryos. The compound is highly toxic to embryos, especially before the development of the placenta. Divalent mercury does not readily cross the placenta, although it does accumulate in the placenta. The disruption in placental function and ensuing embryotoxicity caused by both in vivo and in vitro exposure to $HgCl_2$ provide sufficient evidence that this agent is a developmental toxicant in experimental animals. No specific evidence is available concerning reproductive or developmental effects of $HgCl_2$ in humans.

Most cases of acute toxicity from $HgCl_2$ in humans have been reported following oral ingestion of the compound. Toxic effects include corrosive action on the gastrointestinal tract, followed by renal failure due to necrosis of the proximal tubular epithelium. The mean lethal oral dose for an adult is 1 to 4 g, which corresponds to a blood concentration of about 15 mg Hg/L. The lowest kidney mercury concentration reported for a fatal case of mercury poisoning is 16 mg/kg wet weight.

The most important result of chronic oral exposure to $HgCl_2$ alone is kidney damage, either by necrosis of the proximal tubule or by an autoimmune reaction. A specific form of mercury hypersensitivity called acrodynia or pink disease is occasionally found in children. A genetic component is involved in autoimmune responses to mercury, at least in experimental animals. Neurotoxicity is also a potential risk following chronic exposure to divalent mercury, especially in cases of exposure to mixtures of mercury species.

The binding of divalent mercury to sulfhydryl groups and other biological ligands is responsible for most of the biochemical effects of $HgCl_2$. Mercuric chloride has been found to inactivate many enzymes, induce other enzymes, inhibit polymerization of microtubules, affect membrane permeability, and alter many aspects of cellular and subcellular metabolism. Many of the adverse effects of divalent mercury probably occur as a result of general

metabolic disruption and toxicity to cells and tissues. A summary of some dose-effect relationships of $HgCl_2$ in mammalian systems is given in Table 1-3.

TABLE 1-3. SUMMARY OF EFFECTS OF MERCURIC CHLORIDE ($HgCl_2$) ON MAMMALS OR MAMMALIAN CELLS

Population Studied	Dose ($HgCl_2$)	Effect	Source
Humans			
General population	Acute oral dose, >0.5 g mean, 1 to 4 g	Lethal	G
Children	Dose not certain; usually associated with chronic Hg exposure and with urine Hg levels >50 μg Hg/L	Acrodynia in about 1 in 500 (hypersensitive reaction?)	A,C
Lymphocytes, in vitro	108 μg/L (0.4 μM)	Increased sister chromatid exchange	L O,P
	270 μg/L (1 μM)	No effect (C-mitosis or chromosome aberrations)	P O
	1.4 mg/L (5 μM)	Chromosome aberrations	
	2.7 mg/L (10 μM)	C-mitosis	
Animals, Inhalation Studies			
Mice Pregnant females	0.23 mg/m^3, aerosol (no MMAD given) 4 h/day on Gestation Days 9-12	Chromosome aberrations (structural and numerical), retarded growth, and skeletal abnormalities in embryos	M
Brown Norway rat Male and female	200 to 240 μg/kg/week, aerosol, 2 mo (estimate of minimum air concentration is 1 mg $HgCl_2$/m^3, 1 h/day, 4 days/week for 2 mo)	Autoimmune disease	B
Animals, Other In Vivo Studies			
F344 rat Male	2.5 mg/kg/day, 5 days/week, 104 weeks, gavage	Increased mortality, chronic nephropathy, forestomach hyperplasia, and squamous cell papillomas	S
F344 rat Male and female	5.0 mg/kg/day, 5 days/week, 104 weeks, gavage	Increased mortality, forestomach hyperplasia, squamous cell papillomas, and nasal mucosa inflammation	S
B6C3F1 mice Male and female	5.0 mg/kg/day, 5 days/week, 104 weeks, gavage	Nephropathy	S
Brown Norway rat Male and female	60 μg/kg/week, intratracheal instillation, 2 mo	No effect on kidney	B
Brown Norway rat Male and female	110 μg/kg/week, intratracheal instillation, 2 mo	Autoimmune disease	B

TABLE 1-3 (cont'd). SUMMARY OF EFFECTS OF MERCURIC CHLORIDE ($HgCl_2$) ON MAMMALS OR MAMMALIAN CELLS

Population Studied	Dose ($HgCl_2$)	Effect	Source
Animal, Other In Vivo Studies (cont'd)			
Brown Norway rat Female	2.00 mg/kg/week, im, 39 weeks	Autoimmune disease	J
Brown Norway rat Male and female	3.00 mg/kg/week, oral, 2 mo	Autoimmune disease	B
Mouse embryos	<1.35 mg/kg, iv dose to mother	No effect	H
	1.35 mg/kg, iv dose to mother	Embryotoxicity in vivo	
Syrian hamster Female	8.6 mg/kg, sc, single dose	Chromosome aberrations (bone marrow cells)	Q
	3 to 4 mg/kg/day, sc, during estrous cycle	Delayed or reduced ovulation	Q, U
Mice Male	1.35 mg/kg, ip, single dose	No dominant lethals	K
Rats Male	0.025 μg/kg/day, oral, 12 mo	No dominant lethals	N,R
	0.25 μg/kg/day, oral 12 mo	Dominant lethals	
Animals, In Vitro Studies			
Chinese hamster CHO cells	270 μg/L (1 μM)	Slows cell growth	F
	<2.7 mg/L (<10 μM)	Inhibition of DNA repair and replication	D,E
		Chromosomal aberrations	T
	2.7 mg/L (10 μM)	DNA damage, cell death	D,E
Rat embryos	270 μg/L (1 μM)	CNS abnormalities	I

Sources:

A = Berlin (1986).
B = Bernaudin et al. (1981).
C = Bilderback and Anderson (1975).
D = Cantoni and Costa (1983).
E = Christie et al. (1986).
F = Costa et al. (1982).
G = Gosselin et al. (1984).
H = Kajiwara and Inouye (1986a).
I = Kitchin et al. (1984).
J = Knoflach et al. (1986).
K = Lee and Dixon (1975).
L = Morimoto et al. (1982).
M = Selypes et al. (1984).
N = Vasil'eva et al. (1982).
O = Verschaeve et al. (1984).
P = Verschaeve et al. (1985).
Q = Watanabe et al. (1982).
R = Zasukhina et al. (1983).
S = National Toxicology Program (1993).
T = Howard et al. (1991).
U = Mattison et al. (1983).

The literature contains two studies on the effects of inhalation exposure to $HgCl_2$ on experimental animals. Bernaudin et al. (1981) studied autoimmune disease in rats induced by intratracheal installation (60 to 750 μg/kg/week) for 2 mo and aerosol administration of 5 mL of a 1% $HgCl_2$ solution 1 h/day, 4 days/week for 2 mo. The aerosol exposure resulted in a retention of 50 to 60 μg $HgCl_2$/kg/h. Assuming a rat hourly breathing rate of 0.044 m^3/kg/h (U.S. Environmental Protection Agency, 1988b), the air concentration in the chamber is estimated to have been at least 1,140 μg $HgCl_2/m^3$, (50 μg/kg/h ÷ 0.044 m^3/kg/h = 1,140 $\mu g/m^3$) or roughly 1 mg $HgCl_2/m^3$. Evidence of autoimmune disease was noted for all but the lowest intratracheal exposure (60 μg $HgCl_2$/kg/week). Selypes et al. (1984) found embryotoxic effects in rats exposed to aerosols of 230 μg $HgCl_2/m^3$ for 4 h/day for 4 days during pregnancy.

2. INTRODUCTION

This report is intended to provide a brief review of the available information on the potential health effects associated with exposure to mercuric chloride ($HgCl_2$). The major interest is in potential health effects on the general public from exposure to ambient airborne concentrations of $HgCl_2$. Sources, distribution, fate, and ambient levels of mercuric chloride are reviewed. Data concerning the pharmacokinetics, mutagenicity, carcinogenicity, teratogenicity, and acute and chronic toxicity of $HgCl_2$ are discussed. Mercuric chloride, elemental mercury (Hg), and the numerous other mercury compounds are closely interrelated in terms of their chemistry, their environmental distribution and impact, and their health effects. The distribution and potential health effects of $HgCl_2$ therefore must be considered within the broader context of mercury and mercury compounds in general, with particular attention given to information dealing specifically with $HgCl_2$.

Mercury is not a particularly abundant element, constituting about 2.7×10^{-6} percent of the earth's crust and ranking 74th in abundance of all the elements (Goldwater and Clarkson, 1972). It is found in a number of different minerals (Nriagu, 1979a, lists 24 principal minerals), although only one, cinnabar (HgS), is of great commercial importance. Most of the world's supply of mercury comes from mines in Spain, Yugoslavia, Italy, the Soviet Union, China, Mexico, and the United States (Nriagu, 1979a). United States mercury reserves are located primarily in California and Nevada (SRI International, 1983; Nriagu, 1979a).

Elemental mercury is the only metal that exists as a liquid at room temperatures (melting point −38.9 °C, boiling point 356.6 °C; Berlin, 1986), and it is quite volatile, as are many of its compounds (Singer and Nowak, 1981). Mercury in inorganic compounds exists in one of two oxidation states, +1 (mercurous, Hg_2^{2+}) or +2 (mercuric, Hg^{2+}). Organic mercury compounds contain only the +2 form, bound covalently as either $R\text{-}Hg^+$ or R-Hg-R', where R and R' are organic moieties. Mercuric chloride, Hg_2^{2+}, and Hg^{2+} can all be found in an aqueous solution containing mercury; the representation at equilibrium of each oxidation state is determined by the redox potential of the solution and the presence of compounds that form complexes with the ions (Berlin, 1986).

One distinguishing characteristic of mercury chemistry in general is the tendency of mercury to form covalent rather than ionic bonds (Andren and Nriagu, 1979). Halide salts such as $HgCl_2$ do not ionize readily, and Hg-C bonds (in organic mercury compounds) are stable. Another important chemical feature is that elemental mercury can be readily oxidized to Hg_2^{2+} and Hg^{2+} in some environmental or biological situations, and in others, Hg^{2+} is reduced to Hg_2^{2+} or free Hg^0 (U.S. Environmental Protection Agency, 1984a). In the presence of sulfhydryl groups, Hg_2^{2+} undergoes disproportionation to Hg^0 plus Hg^{2+} (Berlin, 1986). Certain microbial systems also produce methyl mercury (monomethyl mercury, CH_3Hg^+) compounds from Hg^{2+} (U.S. Environmental Protection Agency, 1984a). Methyl mercury is probably the most toxic to humans of any of the mercury compounds. The significance of these reactions is that mercury may enter the environment or a given system in one form (e.g., Hg^{2+} in $HgCl_2$), but, once there, it may be changed into a different form (e.g., CH_3HgCl) having a different potency or type of toxicity. A third major characteristic of mercury chemistry is the affinity of mercury and many mercury compounds for sulfur and sulfhydryl groups. The term "mercaptan" was first used by Zeise in 1834 to describe a particular sulfur-containing compound having a strong affinity for mercury (Goldwater, 1972); "mercaptan" or "mercapto" is now used for any thiol or sulfhydryl group, and "mercaptide" for a metallic salt of a mercaptan. Most of the biochemical effects of mercury or mercury compounds are caused by the binding of the mercury to sulfhydryl groups on various proteins (Berlin, 1986; Goldwater, 1972).

Mercuric chloride, also known as corrosive sublimate, traditionally, has been one of the most important of the many inorganic mercury compounds for use in medicine, agriculture, and chemistry. Existing as white crystals or powder at room temperature, it is one of two chloride salts of mercury; the other is mercurous chloride (Hg_2Cl_2), or calomel. Mercurous chloride, like most mercurous salts, is nearly insoluble in water (0.002 g/L), and probably for that reason has a very low toxicity compared to $HgCl_2$ (solubility in water, 71.5 g/L at 25 °C; Singer and Nowak, 1981). Mercuric chloride is essentially a covalent molecule (Carty and Malone, 1979; MacGregor and Clarkson, 1974). Up to 1,000 °C, gaseous $HgCl_2$ consists of linear monomers (Cl-Hg-Cl) (Carty and Malone, 1979). The predominant species in aqueous solution is undissociated $HgCl_2$ (Carty and Malone, 1979; Brodersen, 1977), although three other complexes of divalent mercury with chloride ions also exist, including

$HgCl^+$, $HgCl_3^-$, and $HgCl_4^{2-}$ (Berlin, 1986; MacGregor and Clarkson, 1974). The serum concentrations of $HgCl_2$, $HgCl_3^-$, and $HgCl_4^{2-}$ are almost equal at normal serum chloride ion concentrations (MacGregor and Clarkson, 1974; see also Carty and Malone, 1979). In contrast to some other mercuric compounds, $HgCl_2$ is not a good source of free Hg^{2+} in solution (Carty and Malone, 1979).

The vapor pressure of $HgCl_2$ is 0.1 mm Hg at 100 °C and 3 mm Hg at 150 °C, and it sublimes at about 300 °C (Singer and Nowak, 1981). The vapor pressure of $HgCl_2$ is less than or nearly equal to that of elemental mercury at temperatures below approximately 180 °C; above 180 °C, $HgCl_2$ has a higher vapor pressure than does mercury (compare values for mercury and $HgCl_2$ in Weast et al., 1986; Singer and Nowak, 1981; Hayes, 1982; and Anonymous, 1978). Mercuric chloride vapor has a high density (9.8 g/cm^3) and dissipates slowly (Singer and Nowak, 1981). Some important chemical and physical properties of $HgCl_2$ are summarized in Table 2-1.

The major uses for mercury (all forms) include electric lighting, wiring devices and switches, batteries, chlor-alkali production, paint manufacture, chemical and allied production, measuring and control equipment, dental equipment and supplies, and laboratory uses. Of these, the principal uses for mercuric chloride include batteries (as raw material in the manufacture of dry-cell batteries), paint (as a preservative agent), and chemical and allied product production (e.g., as a catalyst in organic synthesis or in the preparation of other mercury compounds). From 1989 to 1991, however, there was significant change in the overall demand for mercury among these industries (see Table 2-2). The most dramatic change occurred in the paint industry where demand dropped from 211 tons in 1989 to 7 tons in 1991. Prior to 1991, much larger amounts of mercury were used in paint to preserve the paint film from mildew after the paint is applied to a surface. As of May 1991, all registrations for mercury biocides used in paints were canceled voluntarily by the registrants, thus causing a drastic decrease in the use of mercury in paint (U.S. Environmental Protection Agency, 1993b).

Prior to the late 1980s, most primary batteries and some storage batteries contained mercury in the form of mercuric oxide (HgO), zinc amalgam (Zn-Hg), mercuric chloride ($HgCl_2$), or mercurous chloride (Hg_2Cl_2). As indicated in Table 2-2, from 1989 to 1991,

TABLE 2-1. PHYSICAL AND CHEMICAL PROPERTIES OF MERCURIC CHLORIDE

Property		Source
Code Numbers:	CAS Registry Number: 7487-94-7 RTECS Number: NIOSH/OV9100000 NCI-C60173; UN 1624; TL 898	MEDLARS II (HSDB) (1987) MEDLARS II (RTECS) (1986) Keith and Walters (1985)
Chemical Name:	Mercuric chloride; mercury (II) chloride	Weast et al. (1986) Windholz et al. (1983)
Common Synonyms:	Mercuric bichloride; mercury bichloride; mercury chloride [$HgCl_2$]; mercury dichloride; mercury perchloride; dichloromercury; bichloride of mercury; perchloride of mercury; corrosive mercury chloride; corrosive sublimate; fungchex; MC; calochlor	MEDLARS II (HSDB) (1987) MEDLARS II (RTECS) (1986) Weast et al. (1986) Keith and Walters (1985) Windholz et al. (1983) Weiss (1980)
Chemical Formula:	Cl_2Hg ($HgCl_2$)	
Molecular Weight:	271.50	Weast et al. (1986)
Composition, wt %:	Cl, 26.12 Hg, 73.88	Windholz et al. (1983) Windholz et al. (1983)
Physical State:	Crystals or white granules or powder	Windholz et al. (1983)
Melting Point:	276 °C	Weast et al. (1986)
Boiling Point:	302 °C	Weast et al. (1986)
Heat of Fusion:	15.3 cal/g	Weast et al. (1986)
Refractive Index:	1.859	Weast et al. (1986)
Specific Gravity:	5.44 (25 °C) 4.44 (280 °C)	Weast et al. (1986) Stokinger (1981)
Vapor Density:	9.8 g/cm^3	Singer and Nowak (1981)
Solubility:[a]		Weast et al. (1986)
Water (0 °C)	36 g/L	Windholz et al. (1983)
(20 °C)	69 g/L	Hayes (1982)
(25 °C)	71.5 g/L	Singer and Nowak (1981)
(100 °C)	480 g/L	Stokinger (1981)
Alcohol (25 °C)	330 g/L	
Ether	250 g/L	
Dissociation Constants:	$pK_1 = 6.74$ $pK_2 = 6.48$	Webb (1966)
Partition Coefficients:		Hansch and Leo (1979)
Diethyl ether	log P = −0.58	
Oils	log P = −0.46	

TABLE 2-1 (cont'd). PHYSICAL AND CHEMICAL PROPERTIES OF MERCURIC CHLORIDE

Property		Source
Vapor Pressure:[b]	1.4×10^{-4} mm Hg at 35 °C (solid)	Hayes (1982)
	0.1 mm Hg at 100 °C (solid)	Singer and Nowak (1981)
	1.0 mm Hg at 136.2 °C (solid)	Weast et al. (1986)
	3 mm Hg at 150 °C (solid)	Singer and Nowak (1981)
	10 mm Hg at 180.2 °C (solid)	Weast et al. (1986)
	40 mm Hg at 212.5 °C (solid)	Weast et al. (1986)
	100 mm Hg at 237 °C (solid)	Weast et al. (1986)
	400 mm Hg at 275.5 °C (solid)	Weast et al. (1986)
	760 mm Hg at 304 °C	Weast et al. (1986)
Odor:	None	Weiss (1980)
Taste:	Metallic	Hayes (1982)
Biological Oxygen Demand:	None	Weiss (1980)
Softness Parameter (Chemical Reactivity):	0.064 (Hg^{2+})	Christie and Costa (1983)
Reactivity:		
Does not react with water or with other common materials, stable during transport. Not flammable, but heat from fire may cause formation of toxic fumes of $HgCl_2$. Unstable in the presence of alkalis, decomposed to metallic mercury by sunlight in the presence of organic matter. Readily reduced to mercurous chloride or elemental mercury. Coagulates albumin. With NaOH, produces yellow precipitate. Hg_2^+ can form stable complexes or covalent bonds with organic compounds, including cellular macromolecules.		Christie and Costa (1983) Windholz et al. (1983) Hayes (1982) Weiss (1980)

[a]$HgCl_2$ is also soluble in acetic acid, pyridine, acetone, formic acid, benzene, glycerol, ethyl acetate, and carbon disulfide.

[b]In general, for $HgCl_2$ at temperatures between 0 and 235 °C, $\log V° = 13.28 - (4541/T) - (0.65)(\log T) - 0.00113\ T$, where V° is the vapor pressure in mm Hg and T is the absolute temperature and equal to 273.1 + t (°C).

the use of mercury in battery production decreased 69%, and further reductions were expected in 1992 and 1993 (U.S. Environmental Protection Agency, 1993a).

The figures in Table 2-2 for U.S. consumption of mercury for "other chemical and allied products" includes catalysts for plastics and miscellaneous catalysts. This entire category was reported to have consumed 20 tons of mercury in 1991, which represents about 4% of the total mercury consumed in the United States (U.S. Environmental Protection Agency, 1993a). Mercuric chloride is used as a catalyst in the production of vinyl chloride

TABLE 2-2. COMPARISON OF MERCURY DEMAND WITHIN U.S. MERCURIC CHLORIDE USER INDUSTRIES IN 1989 AND 1991

Industry	Mercury Demand, Mg (tons)	
	1989	1991
Battery	250 (275)	78 (86)
Paint	192 (211)	6 (7)
Other chemical and allied products	40 (44)	18 (20)
Total demand	482 (530)	102 (113)

Source: U.S. Environmental Protection Agency (1993a).

(U.S. Environmental Protection Agency, 1993a). Most of the vinyl chloride produced in the United States (approximately 97.5%), however, is produced via the oxychlorination of ethylene, a process that does not involve mercuric chloride (SRI International, 1991).

Agricultural use of a number of mercury compounds was suspended by the United States in 1970 (specifically alkyl mercury compounds used as seed disinfectants and certain other mercury-based fungicides or slimicides; SRI International, 1983; Singer and Nowak, 1981). Essentially all agricultural use of mercury compounds in the United States was prohibited in 1972 (Singer and Nowak, 1981), as was pharmaceutical use in 1973 (SRI International, 1983).

In the United States in 1991, a total of 102 metric tons of mercury (22% of the total mercury consumption; equivalent to 138 metric tons of pure $HgCl_2$) was used in the production of chemical and allied products, in battery manufacture, and in paints. This figure includes most, if not all, of the $HgCl_2$ used in the United States, but it also includes various other mercury compounds used for these purposes and must therefore be considered a very rough upper limit for total $HgCl_2$ consumption. Total mercury consumption in U.S. industries that consume this and other forms of mercury is estimated to have been 520 tons in 1991 (U.S. Environmental Protection Agency, 1993a). The general trend for consumption of all forms of mercury is downward as efforts are made to decrease mercury emissions, recycle mercury by-products, and replace mercury compounds and processes involving mercury with less hazardous substances and processes (U.S. Environmental Protection Agency, 1993a,b). Although specific figures for the consumption of $HgCl_2$ in the United States are not available,

all indicators point to a decline in $HgCl_2$ use over the past several years, concurrent with the decreased consumption of total mercury.

The OSHA has established a federal occupational exposure standard for mercury of 0.1 mg Hg/m^3 air (1 mg/10 m^3) as a ceiling concentration not to be exceeded at any time during an 8-h shift (Code of Federal Regulations, 1992; official standards for airborne mercury are summarized in Table 1-1). For organic mercury, a time-weighted-average or TWA of 0.01 mg/m^3 was established, with a short-term exposure limit of 0.03 mg/m^3. The American Conference of Governmental Industrial Hygienists (1992) recommended a threshold limit value (TLV) of 0.05 mg/m^3 (TWA) for mercury vapor (all forms except alkyl mercury, which has a TWA of 0.01 mg/m^3 and a short-term exposure limit of 0.03 mg/m^3). For aryl and inorganic mercury compounds only, a TWA of 0.1 mg/m^3 is permitted, although there may be little or no margin of safety at this level (American Conference of Governmental Industrial Hygienists, 1992). Occupational standards in other countries are comparable to the United States (e.g., Czechoslovakia and Sweden, 0.05 mg Hg/m^3 [American Conference of Governmental Industrial Hygienists, 1992]). Although the standards of most countries do not distinguish between mercury and mercury compounds (e.g., $HgCl_2$), Poland has set a separate limit of 0.01 mg/m^3 for elemental mercury and 0.05 mg/m^3 for compounds (American Conference of Governmental Industrial Hygienists, 1992).

A number of books and review articles are available on the health and environmental effects of mercury and mercury compounds in general (World Health Organization, 1976, 1990, 1991; Berlin, 1986; U.S. Environmental Protection Agency, 1984a,b, 1985a,b; Nriagu, 1979b; National Research Council, 1978; Miller and Clarkson, 1973; National Institute for Occupational Safety and Health, 1973; D'Itri, 1972; Friberg and Vostal, 1972; Goldwater, 1972; Hartung and Dinman, 1972; International Atomic Energy Agency, 1972). The occurrences of mercury poisoning in Japan, Iran, and New Mexico provide especially graphic examples of the hazardous potential of mercury in environmental situations. These events resulted from mercury contamination of water and of seed-grain accidentally used for food. The present report, within the limits of available information, details the effects on human health that can be expected from exposure to $HgCl_2$. Whenever possible, these health effects of $HgCl_2$ have been correlated with exposure to ambient, airborne concentrations;

much of the available data, however, concerns occupational concentrations or oral and in vitro routes of exposures for experimental animals.

3. AIR QUALITY AND ENVIRONMENTAL FATE

3.1 SOURCES

3.1.1 Natural Occurrence

One of the largest sources of airborne mercury is the natural degassing of the earth's crust, particularly in regions with mercury-rich soils or mineral deposits (World Health Organization, 1991; Matheson, 1979). Geothermal activity such as volcanoes and hot springs also contributes mercury to the air (Nriagu, 1989; Lindqvist and Rodhe, 1985). Natural emissions of mercury in Hawaii include both gaseous and particulate mercury, and the gaseous mercury includes both Hg^0 and Hg^{2+} (Siegel and Siegel, 1979). The anionic species accompanying Hg^{2+} is dependent on regional availability; in Hawaii, $HgCl_2$ and Hg^0 are the two biologically significant natural geothermal forms of gaseous mercury. Both mercury vapor (Hg^0) and organic mercury compounds are released to the atmosphere from soils; the amount varies with soil type and location (Grant et al., 1991; Siegel and Siegel, 1979; Rogers, 1978). The mercury vapor may be from either accumulated elemental mercury or the reduction of inorganic mercury compounds by organic matter or organisms. Increased levels of mercury, as either mercury vapor or organic mercury, are found in the air over soils to which $HgCl_2$ or other inorganic mercury compounds have been added experimentally (Matheson, 1979; Rogers, 1978; Johnson and Braman, 1974). Recent estimates indicate that total natural emissions of mercury are of the order of 2,500 metric tons/year (Nriagu, 1989).

3.1.2 Anthropogenic Sources

Mercury from anthropogenic sources was thought at one time to account for just 25 to 30% of the annual atmospheric mercury worldwide (Matheson, 1979; Miller and Buchanan, 1979; Watson, 1979). Current estimates, however, indicate that anthropogenic sources of mercury may be responsible for 30 to 75% of the total yearly input to the atmosphere from all sources, or between 2,000 and 4,500 metric tons/year (Lindqvist et al., 1991; Fitzgerald, 1994). Increasing anthropogenic activities may account for increases in global atmospheric mercury during the past few decades (Slemr and Langer, 1992). Mercury emissions to the

atmosphere are estimated at 332 metric tons/year in the continental United States (U.S. Environmental Protection Agency 1993a,b). Table 3-1 illustrates the relative contributions of the most prominent sources to total atmospheric emission of Hg^0 and $HgCl_2$ in the United States.

TABLE 3-1. ESTIMATED 1990 NATIONWIDE MERCURY EMISSIONS FOR SELECTED SOURCE CATEGORIES

Source Category	Mercury Emissions (tons/year)
Mercury and Mercury Compound Production	
Secondary mercury production	6.3
Major Uses of Mercury	
Chlor-alkali production	10.2
Battery manufacture[a]	0.1
Electrical uses	9.9
Combustion Sources	
Coal combustion	122.0
Oil combustion	14.9
Natural gas combustion	0
Municipal waste combustion[a]	63.8
Sewage sludge combustion	1.8
Medical waste combustion[a]	64.7
Wood combustion	0.3
Miscellaneous Manufacturing Processes	
Portland cement production	6.2
Lime manufacturing	0.7
Carbon black production	0.2
By-product coke production	NA
Primary lead smelting	9.0
Primary copper smelting	NA
Petroleum refining	NA
Oil shale restoring	0
Geothermal power plants	1.4
Other Miscellaneous Sources	
Mercury catalysts	0
Dental alloys	0.6
Mobile sources	5.0
Crematories	0.4
Paint	14.6
Total	332.0

[a]Industries for which a significant fraction of emissions is expected to be $HgCl_2$.

Source: U.S. Environmental Protection Agency (1993a).

Anthropogenic sources of atmospheric mercury include mining and smelting operations (both of mercury and of several other metals); production and consumption of mercury-containing goods such as paint and batteries; production processes that involve mercury, such as chlor-alkali production; and the burning of fossil fuels, which contain varying amounts of mercury. The largest sources of anthropogenic mercury discharges to the environment are generally point-source emissions such as the burning of fossil fuels (particularly coal) and refuse incineration. The mercury emitted from the coal combustion process is thought to be primarily mercury vapor and mercuric oxide (Lindqvist et al., 1991). Metzger and Braun (1987) and Collins and Cole (1990) have reported that the majority of the mercury emitted from municipal solid waste incineration (80 to 90%) is in the form of $HgCl_2$, with some mercurous chloride also present. Reduced emissions of mercury are expected as this industry makes use of spray dryer scrubber, high-efficiency particulate-control devices equipped with charcoal filters (Rothstein et al., 1991; Lindqvist et al., 1991).

3.2 DISTRIBUTION AND FATE

Simulations of the global mercury cycle have generally shown the atmosphere to be the primary vehicle for the distribution of mercury at the surface of the earth (Fitzgerald and Clarkson, 1991; National Research Council, 1978; Lindqvist and Rodhe, 1985). Using estimated emission factors for different source categories, the overall distribution for anthropogenic emissions within North America has been calculated to be 81% Hg^0, 17% Hg^{2+}, and 2% particulate mercury (Bloxam and Petersen, 1990). These estimates have been used to model the long-range transport, transformation, and deposition of mercury (Bloxam et al., 1991). Mercury emitted from incinerators or power plants as Hg^{2+} is readily scavenged and dry deposited. Theoretically, $HgCl_2$ and other mercuric mercury compounds also may be reduced to mercury in the atmosphere (Schroeder et al., 1990); however, no experimental studies of such reactions have been performed under conditions relevant to the atmosphere. Given the low observed values of air Hg^{2+} and particulate mercury concentrations, model runs have been performed assuming no net gas-phase chemistry (i.e., reduction reactions are assumed to nearly balance oxidation reactions) (Bloxam et al., 1991). Elemental mercury can be transported great distances in the atmosphere, as is evident from

the detection of elevated mercury levels in fish from areas far from any known mercury sources (Tomlinson and McLean, 1976, cited in Miller and Buchanan, 1979; Fitzgerald and Watras, 1989; Wiener et al., 1990; see also World Health Organization, 1976).

Atmospheric mercury may be deposited to and revolatilized from both land and water many times, therefore effectively being recycled. The effective residence time for mercury vapor in continental air has been estimated to be up to 3 years if this recycling is taken into account (World Health Organization, 1991; Miller and Buchanan, 1979). Other estimates for atmospheric residence time, that do not necessarily allow for recycling, range from 5.5 to 90 days (Andren and Nriagu, 1979; Miller and Buchanan, 1979; National Research Council, 1978). Mercuric chloride is probably recycled proportionately less than total mercury because at least some of the $HgCl_2$ deposited on the land or in water is transformed to Hg^0 or organic mercury. This would result in a shorter effective atmospheric residence time for $HgCl_2$ than for total mercury.

Precipitation is thought to be a major route for removal of mercury from the air. However, dry deposition of Hg^0 and Hg^{2+} does occur to a lesser extent. Recent studies suggest there is a measurable dry deposition rate of mercury to forests (Lindberg et al., 1991, 1992), which increases in the summer ($\approx$0.03 cm s^{-1}) and decreases in the winter ($\approx$0.001 cm s^{-1}).

Both inorganic and organic forms of mercury are subject to conversion in the environment (particularly in water or soil) by either chemical and physical or biologically mediated processes (World Health Organization, 1990). Ionic mercury (Hg^{2+}) can be formed in the environment by oxidation of metallic mercury vapor (Hg^0) or by the breakdown of various organic mercury compounds. The ionic mercury, depending on local conditions such as the presence of certain bacteria, can be reduced to elemental mercury, form complexes and chelates with organic materials, or be converted to methyl mercury and other organic mercury compounds. Aqueous $Hg(OH)_2$ is reduced when irradiated with simulated sunlight; however, $HgCl_2$ is stable under these conditions (Munthe and McElroy, 1992).

These conversion reactions can have a significant effect on the distribution of mercury species, particularly on the local level. Perhaps, the most important of these processes is the methylation of inorganic mercury by bacteria in aquatic sediments. Methyl mercury

compounds, which are probably the most toxic forms of mercury to man, accumulate in fish in mercury-polluted waters, no matter what the actual mercury species might be (U.S. Environmental Protection Agency, 1979; World Health Organization, 1990). The ratio of the methyl mercury concentration in fish tissue to the concentration of inorganic mercury in water is usually between 10,000 and 100,000 to one (World Health Organization, 1991). Divalent inorganic mercury (e.g., in $HgCl_2$) will not necessarily remain as divalent inorganic mercury, but may be transformed in the environment to elemental or organic mercury, including methyl mercury compounds.

3.3 AMBIENT LEVELS

Atmospheric mercury levels over nonmineralized (i.e., non-ore-bearing) rural areas range from <0.005 to 2 ng/m^3 (mean, 0.15 ng/m^3) particulate mercury and 1 to 10 ng/m^3 (mean, 4.0 ng/m^3) total volatile mercury (Grant et al., 1991; Schroeder, 1982; Matheson, 1979; National Research Council, 1978). Total gaseous mercury over the Atlantic Ocean (7 to 54° N) ranged from 1 to 2.6 ng/m^3 (mean, 1.763 ng/m^3) in October 1977 to 1.41 to 3.41 ng/m^3 (mean, 2.247 ng/m^3) in October 1990 (Slemr and Langer, 1992), reflecting an increase of about 1.46 ± 0.17%/year. Total mercury levels (particulate + volatile) in ore-bearing terrestrial areas range from 7 to 20 μg/m^3 and in volcanic areas from 20 to 37 μg/m^3 (Schroeder, 1982; National Research Council, 1978). Particulate mercury levels in urban areas range from <0.01 to 220 ng/m^3 (mean, 2.4 ng/m^3) and volatile mercury levels from 0.5 to 50 ng/m^3 (mean, 7.0 ng/m^3). In areas around industrial point sources such as chlor-alkali plants, thermometer factories, smelters, and mercury mines, total atmospheric mercury levels up to 5 mg/m^3 have been observed (Schroeder, 1982; National Research Council, 1978). Mercury levels in the air are affected by local variations in mercury emanations from land or water, distance above ground, wind speed and direction (e.g., from the direction of a mercury emission source), and ambient temperature. The average or background concentration of total atmospheric mercury in regions away from point sources has been estimated to be 1 to 2 ng Hg/m^3 air in rural areas (U.S. Environmental Protection Agency, 1984a) and up to 10 ng/m^3 (U.S. Environmental Protection Agency, 1984a) or

20 ng/m^3 (Berlin, 1986) in urban areas. Mean atmospheric mercury concentrations for large cities in the United States ranged from 10 to 170 ng/m^3 (Gerstner and Huff, 1977).

The principal mercury species reported to occur in the atmosphere are elemental mercury vapor (Hg^0), mercuric chloride vapor ($HgCl_2$) and possibly some other volatile inorganic compounds, organomercury compounds such as methyl mercuric chloride (CH_3HgCl) and dimethyl mercury [$(CH_3)_2Hg$], and particulate mercury of unknown chemical species (Schroeder, 1982). Only a few studies have attempted to distinguish various chemical forms of mercury in the atmosphere, and most available measurements of atmospheric mercury content are of particulate mercury alone, mercury vapor or volatile mercury (of whatever chemical species) alone, or total mercury (particulate + vapor).

The atmospheric mercury in one urban area (Tampa, FL) was found to include, on the average, 49% Hg^0, 25% mercuric halides (including but not limited to $HgCl_2$), 21% monomethyl mercury compounds, 4% particulate mercury, and 1% dimethyl mercury (Johnson and Braman, 1974; Matheson, 1979; National Research Council, 1978). The concentration of mercury as Hg^{2+} varied from 0 to 220 ng Hg/m^3 air, and from 0 to 75% of total atmospheric mercury (Johnson and Braman, 1974). Due to the age of these reports, the state-of-the-art at the time, the strong potential for contamination of samples during transport, and artifacts in sampling media, these data should be viewed cautiously.

As part of more recent work aimed at developing analytical methods for the determination of mercury species in the atmosphere, Schroeder and Jackson (1985, 1987) determined gaseous and particulate-phase levels of mercury at four locations (urban and rural sites influenced by various potential sources of mercury including a coal-fired power plant, waste incineration operations, and a battery manufacturing plant) in and around Toronto, Canada, over a 3-week period during the fall of 1981. Using a Barringer mercury monitor, they determined that elemental mercury comprised 75 to 96%, and mercuric chloride accounted for just 0 to 3% of total vapor-phase mercury at the four sites. Particulate mercury accounted for just 0.4 to 3.3% of the total atmospheric mercury at the four sites. Levels of airborne $HgCl_2$ from 0 to 2.4 ng Hg/m^3 were measured. Total mercury levels varied from 3 to 114 ng/m^3.

In short, atmospheric mercury levels, both of total mercury and of inorganic mercury, may vary considerably with the degree of industrialization and the proximity to various

natural and anthropogenic point sources of mercury. The amount of inorganic mercury present is probably not a constant fraction of the total amount of mercury. If one assumes that the total mercury concentration in an urban area is 10 ng/m^3 and that an average of 19% of the mercury is inorganic mercury (Hg^{2+}; U.S. Environmental Protection Agency, 1984a), an estimate of 1.9 ng/m^3 for the average ambient concentration of inorganic mercury is obtained. If all of the inorganic mercury were $HgCl_2$, this would correspond to an ambient level of 2.6 ng $HgCl_2$/m^3 air. The data of Schroeder and Jackson (1987) suggest that the actual proportion of airborne mercury present as $HgCl_2$ may actually be considerably lower (<3%). Information on indoor (nonoccupational) concentrations of mercury or $HgCl_2$ was not available.

3.3.1 Exposure

Most available studies (and many of the analytical techniques used) fail to distinguish between various forms of mercury, or at best distinguish only between organic and inorganic mercury. For this reason, information on exposure to $HgCl_2$ cannot always be separated from available information on exposure to total mercury or to total inorganic mercury. However, because of the known interconversions of mercury species in the environment and the rarity of exposure to a single mercury compound, information on exposure to total mercury and to the general types of mercury must also be considered in assessing actual or potential health effects of $HgCl_2$ on humans.

In 1985, the NIOSH estimated that 20,293 people (including 10,062 women) were exposed to $HgCl_2$ from occupational use of the compound (MEDLARS II, HSDB, 1987). The NIOSH also estimated that 51,024 people were potentially exposed to $HgCl_2$ through actual use of $HgCl_2$ (25%), use of trade name products known to contain $HgCl_2$ (1%), or use of certain types of products that may contain $HgCl_2$ (74%; MEDLARS II, HSDB, 1987). It is not known what products were involved or whether this figure included people with occupational exposure to $HgCl_2$. Based on assumptions of an inhalation volume of 10 m^3/working day and exposure to mercury at the OSHA limit of 0.1 mg/m^3, the maximum expected inhalation of mercury by an occupationally exposed adult is 1.0 mg of mercury

(as elemental or inorganic mercury) in a working day. If all the mercury were in the form of $HgCl_2$, this would mean a maximum inhalation of 1.35 mg $HgCl_2$/day.

Although local concentrations of mercury and $HgCl_2$ may be very high in some industrialized areas (up to 5 mg/m^3), the general public probably encounters a maximum of 10 to 20 ng total Hg/m^3 air in urban areas and as little as 1 to 2 ng/m^3 in rural areas (see Section 3.3). To assess human inhalation exposure to mercury, it would be necessary to know concentrations in microenvironments, including indoors and relate this to activity patterns. However, this information is not available. The World Health Organization (1990) estimates an average daily intake of inorganic mercury by air of 2 ng/day. Total intake of atmospheric mercury will be considerably higher near point sources, but the proportion of $HgCl_2$ and therefore the amount of $HgCl_2$ inhaled will depend on the specific type of point source.

The general public also is exposed to mercury and mercury compounds in drinking water and food (U.S. Environmental Protection Agency, 1984a, 1985b). The average human intake of mercury from drinking water has been estimated to be 50 ng/day; this figure is based on an average mercury concentration in noncontaminated drinking water of 25 ng/L and a daily water intake of 2 L for an adult (U.S. Environmental Protection Agency, 1984a). Most of this mercury is thought to be inorganic mercury (Hg^{2+}), although as much as 30% may be methyl mercury (U.S. Environmental Protection Agency, 1984a).

Food (seafood, in particular, in the case of organic mercury) may be the major source of mercury for people who are not occupationally exposed to it. The average adult ingests 3,200 ng (3.2 μg) inorganic and organic Hg/day in their diet (Grant et al., 1991). Grant et al. (1991) estimate that recreational fishermen may consume as much as 70 μg/day total mercury in fish (7μg as inorganic and 63 μg as methyl mercury) and populations (e.g., Native Americans) that rely on fish as their principal food source may consume about 216 μg/day total mercury in fish (21.6 μg as inorganic and 194.4 μg as methyl mercury). Due to the predominant source of mercury in these subpopulations (i.e., freshwater fish from acidified ponds and lakes), inorganic mercury content is likely less than 10%, and methyl mercury content is likely to approach 90% of the total mercury (Grant et al., 1991). When gastrointestinal absorption rates of inorganic and methyl mercury are considered (7 and 90%,

respectively), the average adult is found to retain more methyl mercury from food than inorganic mercury (see Table 1-2).

Another source of exposure to mercury, principally elemental mercury, is dental amalgam fillings. Amalgams used for dental restorations generally contain approximately 50% mercury at the time of mixing with various silver alloys. The release of elemental mercury vapor from dental amalgams has been known for over a half a century (World Health Organization, 1991; Clarkson et al., 1988). Exposure to inorganic mercury can occur through corrosion of the amalgam material into saliva or ingestion of amalgam particles abraded from restored surfaces (U.S. Public Health Service, 1992; Eley and Cox, 1988; Brune, 1986). Several reviews document the difficulties associated with making accurate estimations of the amount of each mercury species released and the resultant mercury uptake by the human body (Olsson and Bergman, 1992; U.S. Public Health Service, 1992; World Health Organization, 1991; Berglind, 1990; Clarkson et al., 1988). Factors that influence the release of mercury include bruxism (i.e., teeth grinding), chewing, number of amalgams, and the use of sealants. Estimates of daily mercury absorption from dental amalgam restorations range from 1.2 to 29 μg for mercury vapor and 0 to 2 μg for inorganic mercury (U.S. Public Health Service, 1992; Olsson and Bergman, 1992; World Health Organization, 1990).

Ranges of estimates from recent EPA, WHO, and U.S. Public Health Service documents for daily intake and retention of total mercury and mercury compounds by the general population (not occupationally exposed) are depicted in Table 1-2. These estimates indicate that the hypothetical adult would have an estimated total daily intake of between 5.7 and 63 μg Hg/day, including 3.9 to 24.6 μg Hg/day as inorganic mercury, 1.5 to 36 μg/day as Hg^0, and 0.3 to 2.4 μg/day as methyl mercury. The estimated amount of mercury absorbed will be considerably less: 0.26 to 1.7 μg Hg as inorganic mercury, 1.2 to 29 μg Hg^0, and 0.3 to 2.3 μg organic mercury, for a total of 1.8 to 33 μg Hg absorbed/day. If all of the inorganic mercury is assumed to be $HgCl_2$, this amounts to an estimated intake of between 5.3 and 33 μg $HgCl_2$/day for an adult; the amount of absorbed $HgCl_2$ is between 0.4 and 2.3 μg $HgCl_2$/day. For a 70 kg adult, the estimated total absorbed dose of inorganic mercury would be 4 to 24 ng Hg/kg/day, or 6 to 33 ng $HgCl_2$/kg/day if all the inorganic mercury were in the form of $HgCl_2$.

Some people also are exposed to $HgCl_2$ or other mercury compounds through the use of various skin ointments (Bourgeois et al., 1986; Dyall-Smith and Scurry, 1990) and soaps (Lauwreys et al., 1987). United States Food and Drug Administration regulations limit the concentration in bleaching creams to 0.2% (Burge and Winkelmann, 1970). Peritoneal lavage with $HgCl_2$ solutions (0.1 to 0.2%) has been used in some types of cancer surgery in an effort to prevent recurrence of the cancer (Gelister et al., 1985; Laundy et al., 1984; Umpleby and Williamson, 1984; Dick, 1983; Elliott and Dale, 1983; Lai et al., 1983). Several cases of mercury poisoning (including several fatalities) have resulted from this practice; for this reason and because $HgCl_2$ is not the most effective agent for killing cancer cells, this use of $HgCl_2$ has been discontinued (Gelister et al., 1985; Laundy et al., 1984; Dick, 1983; Elliott and Dale, 1983; Lai et al., 1983). Accidental ingestion of $HgCl_2$ does occur occasionally, however, and can be fatal (Giunta et al., 1983; Stack et al., 1983; Samuels et al., 1982; Winek et al., 1981).

4. PHARMACOKINETICS

4.1 ABSORPTION

Specific information on the absorption of inhaled inorganic mercury compounds such as $HgCl_2$ is lacking, although absorption of approximately 40% is estimated in dogs (Clarkson, 1989). The EPA assumed a retention factor of 0.8 (80%) for all forms of nonparticulate mercury (elemental mercury vapor, inorganic ionic mercury, and methyl mercury compounds) in estimating mercury dosages from inhalation (U.S. Environmental Protection Agency, 1984a). Inhalation of suspended dusts or aerosols of inorganic mercury compounds can also occur (most likely in an occupational setting), and deposition and absorption of mercury is then dependent primarily on the size of the particles and the solubility of the compounds involved (Chang, 1980; Gerstner and Huff, 1977).

Absorption of mercuric compounds from the mammalian gastrointestinal tract is generally less than 20% and may be as low as 2%, depending at least in part on the solubility of particular compounds (Berlin, 1986; Sin et al., 1983; Chang, 1980; Gerstner and Huff, 1977; Clarkson, 1972, 1973). Up to 15% of mercury administered as protein-bound mercuric nitrate was retained by human volunteers (Chang, 1980; Clarkson, 1972). The EPA has used estimates of 10% (U.S. Environmental Protection Agency, 1984a) and 7% (U.S. Environmental Protection Agency, 1988a) absorption of inorganic mercury from water or food sources. These estimates were based on studies that may not have accounted adequately for possible rapid excretion of absorbed mercury during the experimental period. Nielsen (1992) has estimated an absorption rate of 20% from whole body retention data obtained from mice given single oral doses at two different dose levels. Regardless of the absorption rate assumed, food provides most of the inorganic mercury absorbed by a typical nonoccupationally exposed person. Gastrointestinal absorption of $HgCl_2$ in rats is dependent on pH (increased absorption with increased pH) and on the region of the gastrointestinal tract involved, and it seems to be correlated with binding to an unknown protein (Endo et al., 1984, 1986). Absorption of $HgCl_2$ may be increased at high doses due to its corrosive action on the gastrointestinal tract (Berlin, 1986; Gerstner and Huff, 1977). Increased absorption of inorganic mercury compounds and other heavy metals from the gastrointestinal tract has also

been observed in suckling animals, including nonhuman primates, but similar data are not available for humans (Berlin, 1986; Lok, 1983; Webb, 1983; Walsh, 1982; Jugo, 1979).

Absorption of $HgCl_2$ or other mercuric compounds across the skin has also been demonstrated (Baranowska-Dutkiewicz, 1982; Chang, 1980; Gerstner and Huff, 1977; Burge and Winkelman, 1970). Available information from animal studies indicates that up to 6 or 8% of $HgCl_2$ may be absorbed (Berlin, 1986; Chang, 1980), and the rate of absorption is related to concentration and inversely related to time (Baranowska-Dutkiewicz, 1982). Skin exposure to mercury compounds may occur with solutions, ointments, and suspended dusts or aerosols, but, especially for the latter source, the relative importance of skin exposure versus inhalation has not been established.

The major route of exposure to elemental mercury is inhalation of the vapor, of which about 70 to 80% may be absorbed (Berlin, 1986; Cherian et al., 1978, Gerstner and Huff, 1977). Although elemental mercury can be absorbed through the skin (Winship, 1985), this is probably a far less important route of exposure than is inhalation (Berlin, 1986; Gerstner and Huff, 1977). Essentially, no mercury is absorbed from the gastrointestinal tract following ingestion of elemental mercury unless soluble oxides or sulfides are formed (Winship, 1985). Mercurous (Hg_2^{2+}) compounds are generally less soluble than mercuric compounds and are therefore less likely to be absorbed by the body (Gerstner and Huff, 1977). In some cases, they may be oxidized to form soluble and therefore more absorbable compounds (Winship, 1985). The major route of exposure to organic mercury, particularly methyl mercury compounds, is through absorption from food (especially fish); between 90 and 100% of ingested methyl mercury and 80 to 100% of organic mercury compounds in general are absorbed from the gastrointestinal tract (U.S. Environmental Protection Agency, 1984a; Chang, 1980; Clarkson, 1973). About 80% of inhaled organic mercury and 6% of methyl mercury applied to skin may also be absorbed (Berlin, 1986; Chang, 1980).

4.2 RETENTION AND DISTRIBUTION

Mercuric chloride does not dissociate readily in aqueous solution (Carty and Malone, 1979). However, on entering the bloodstream, the mercuric ions may enter reversible complexes with ligands other than Cl^-, such as the sulfhydryl groups of proteins (Carty and

Malone, 1979; Gerstner and Huff, 1977). Essentially no free or ultrafilterable mercury is found in the blood. Most of the ions are bound either to albumin or other protein fractions of the plasma (Winship, 1985; Gerstner and Huff, 1977) or to the membranes and proteins (such as hemoglobin) of the erythrocytes (Berlin, 1986; Gerstner and Huff, 1977).

The ratio of erythrocyte mercury to plasma mercury in man is between 1 to 1 and 1 to 2.5 several hours after parenteral, oral, or inhalation exposure to inorganic mercury compounds or elemental mercury (Berlin, 1986; Chang, 1980; Gerstner and Huff, 1977; MacGregor and Clarkson, 1974; Clarkson, 1972), although immediately following inhalation of elemental mercury, it may be as high as 40 to 1 (Cherian et al., 1978). The corresponding distribution of mercury in humans exposed to organic mercury compounds may be 10 or 20 to 1, and in some mammalian species it may be as high as 300 to 1 (Chang, 1980; Gerstner and Huff, 1977; MacGregor and Clarkson, 1974; Clarkson, 1972). This difference in distribution may be related to differing abilities of organic mercury and the mercuric ion to form stable complexes in the plasma (MacGregor and Clarkson, 1974). The clinical significance of the different distribution of mercury types in the blood is that it permits diagnosis of the type of mercury to which an individual has been exposed, although because of such factors as the biotransformation of mercury in the body, the accuracy of diagnosis may decrease with time following exposure (Gerstner and Huff, 1977). Short-chain alkyl mercury compounds such as methyl- or ethylmercury are very stable in the body, whereas long-chain compounds may be metabolized over time to the mercuric ion; the mercury distribution in the blood therefore may shift from a distribution characteristic of organic mercury compounds to one more suggestive of inorganic compounds. Elemental mercury and monovalent mercury are also oxidized to the mercuric ion in the bloodstream (Berlin, 1986; Chang, 1980; Gerstner and Huff, 1977). The ratio of erythrocyte to plasma mercury concentration, together with blood levels of mercury, can be used to calculate the body burden of short-chain alkyl mercury compounds but not that of mercury from inorganic or long-chain organic compounds (Gerstner and Huff, 1977).

The distribution of divalent mercury in the body and within organs varies with species, strain, route of exposure, dose, and time following exposure. In general, most of the divalent mercury in the body is concentrated in the proximal convoluted tubules of the kidneys and to a lesser extent in the liver (Nielsen and Andersen, 1990; Berlin, 1986;

Winship, 1985; Gerstner and Huff, 1977; MacGregor and Clarkson, 1974). However, Bernaudin et al. (1981) observed effects (granular fixation patterns) normally observed in the kidneys of rats exposed by other routes in the lungs and spleens of rats exposed intratracheally to $HgCl_2$ for 2 mo. At the lowest dose tested, these effects were observed in the lungs and spleens, but not in the kidneys, suggesting that the kidneys may not be the preferential site of deposition following inhalation exposure. Within a day, after 5 days of subcutaneous exposures to 1.4 mg $HgCl_2$/kg/day, mean kidney levels of mercury (micrograms per grams of tissue) in five rats were 78 times higher. However, Nielsen and Andersen (1990) found that the relative deposition (percentage of residual body burden) of mercury in the liver, stomach, and spleen 14 days after a single ip injection of $HgCl_2$ tended to increase with increasing doses (ranging from 13.6 to 1,360 μg $HgCl_2$/kg) in two strains of mice, but tended to decrease with increasing dose in kidneys, lungs, and brain. Therefore, whereas the kidney remained the major depot besides the carcass, the ratio between the mercury burden in the kidneys and liver ranged from 4.4 at the low dose to 1.7 at the high dose. Following gavage dosing, the combined relative deposition in kidneys and liver is not markedly different (Nielsen and Andersen, 1989, 1990), but, in one mouse strain, the kidneys to liver ratio was 2.5 at a dose of 0.27 mg $HgCl_2$/kg and 0.8 at a dose of 27 mg $HgCl_2$/kg. Therefore, within several hours after parenteral administration of inorganic mercury, kidney mercury levels may be as much as 300 times greater than blood levels, and the kidneys retain mercury longer than other tissues (Clarkson, 1972). The liver contains the next highest concentration of inorganic mercury, and mercury may also accumulate in the mucous membranes of the intestinal tract and the epithelium of the skin, the spleen, and certain tissues in the testes and the brain (Berlin, 1986).

In contrast to mercury vapor and methyl mercury compounds, divalent mercury does not readily cross either the blood-brain or placental barriers, although some divalent mercury does accumulate in the placenta, fetal membranes, and amniotic fluid, as well as the frontal and basal cerebral regions of the brain (Berlin, 1986; Winship, 1985). Brain mercury levels following a single injection of divalent mercury may be approximately 10 times as high as blood levels, but are still substantially lower than brain levels found following injection or inhalation of mercury vapor or organic mercury (Clarkson, 1972; see also Ogata et al., 1985; Chang, 1980; Berlin et al., 1969). Intraperitoneal injection of $HgCl_2$ results in an uneven

distribution of mercury within the different anatomical structures of the brain. At the cellular level, the largest accumulation of mercury was seen in the spinal cord neurons. Ultrastructurally, mercury deposits were located exclusively in lysosomes (Schionning and Moller-Madsen, 1991; Moller-Madsen, 1990). The same pattern of mercury central nervous system distribution occurs following oral administration (Moller-Madsen, 1990). Experiments in rats and mice have shown that intramuscular injection of inorganic mercury results in retrograde axonal transport and accumulation of Hg^{2+} in motor neurons (Arvidson, 1990).

The half-life of inorganic mercury in the human body is between 1 and 2 mo, although for certain organs, particularly the kidneys and brain, the retention times are somewhat longer (Berlin, 1986; Cherian et al., 1978; Gerstner and Huff, 1977; Clarkson, 1972). The kidney is considered the critical target organ in cases of oral and parenteral exposure (especially acute exposure) to inorganic mercury; for exposure to elemental mercury, alkyl-mercury components such as methyl mercury, mixtures of mercury species, or chronic low doses of inorganic mercury, the nervous system is the critical target organ (Berlin, 1986; Jugo, 1979; Chang, 1980). Due to the lack of pulmonary toxicity studies, the importance of the lung as a target organ is unknown.

In rats exposed to 2 to 3 subcutaneous doses of $HgCl_2$, 70 to 84% of the mercury found in the kidney was bound to metallothionein, a low molecular weight cytoplasmic protein rich in sulfhydryl groups (Piotrowski et al., 1974). Studies with $HgCl_2$ indicate that mercuric mercury, like other divalent cations such as cadmium, zinc, and copper, can induce the synthesis of metallothionein (Lee et al., 1983; Piotrowski et al., 1974). However, unlike cadmium, mercuric mercury appears to induce metallothionein production in kidney cells without impacting synthesis of metallothionein in the liver (Piotrowski et al., 1974).

The transport and distribution of inorganic mercury are different in suckling animals than in adult animals; considerably more mercury (13- to 19-fold) is accumulated in the liver and brain of the suckling animal than in the adult, presumably because the kidneys bind the mercury less well in the young animal (Jugo, 1979). This could be due, in part, to an elevated store of hepatic metallothionein (Daston et al., 1984). Hepatic metallothonein concentration has been reported to be 8- to 20-fold higher in prenatal rats than in postweaning animals (Bell, 1980; Wong and Klaassen, 1980). Although renal damage is generally of

much greater concern in acute exposures, nervous system damage does occur from inorganic mercury poisoning; therefore, it seems likely that very young children might be at a much greater risk for nervous system toxicity from inorganic mercury exposure than are adults, even though specific data are not available for humans (Jugo, 1979).

Although high blood levels of mercury among members of a population generally indicate high exposure of the population, individual exposure to or body burden of inorganic mercury cannot necessarily be estimated from blood or urine concentrations (Gerstner and Huff, 1977). In particular, mercury concentrations in target organs such as the kidneys and nervous system cannot be calculated from blood levels. Blood mercury levels in normal individuals having no known occupational or other specific source of exposure vary considerably and are not correlated with age, sex, or body weight (Gerstner and Huff, 1977). Reported values in these individuals range from 5 to 100 μg Hg/L (Stokinger, 1981). The upper limit of "normal" is currently considered to be 30 μg Hg/L blood (0.03 mg/L), based on a study of 812 blood samples from 15 countries (Goldwater, 1972; see also Stokinger, 1981; Gerstner and Huff, 1977; 95% of the samples had mercury levels less than 30 μg/L). Gerstner and Huff (1977) suggest that a level of 10 μg/L is an acceptable upper limit for healthy populations.

Schroeder (1971) lists a blood mercury level of 5 μg/L (0.005 mg/L) for a 70-kg reference man. This man also has kidney, brain, lung, and liver mercury concentrations of 2.81, 1.0, 0.58, and 0.3 mg/kg wet weight, respectively, and a total body burden of approximately 13 mg Hg (about 0.19 mg/kg wet weight). Joselow et al. (1967) found an average of 2.75 mg Hg/kg wet weight in kidney tissue (maximum, 26.3 mg/kg) from 39 autopsies of humans with no known mercury exposure. Liver concentrations averaged 0.30 mg/kg and brain 0.10 mg/kg (maximum, 0.9 and 0.6 mg/kg, respectively), and tissue mercury levels did not appear to be related to age. In an analysis of tissue samples from 113 human autopsies, Mottet and Body (1974) found that 70% of the bodies contained total mercury burdens of less than 0.25 mg/kg wet weight, and only 6% had levels higher than 0.75 mg/kg. The most variable tissue was the kidney, which had an average mercury burden of approximately 0.75 mg/kg wet weight (29% of the samples were higher than this); liver and lung contained 0.25 mg/kg on the average, and cerebellum approximately 0.13 mg/kg. People from urban populations contained a statistically higher level of mercury than did

people from rural populations, but no correlation was found between tissue mercury levels and age (range, 26 weeks of gestation to 88 years).

Several additional studies of mercury levels in human tissues were reviewed by Mottet and Body (1974) and Goldwater (1972). Although tissue mercury levels vary among studies (probably due to differences in analytical techniques), in all cases, the highest mercury concentrations in the body were found in the kidneys. These data suggest that average body burdens of mercury are 10 to 100 times higher than the concentrations in blood; mercury concentrations are higher in the kidneys than in other tissues and are approximately 3 to 10 times higher than total body mercury concentrations. It should be noted that these values (for blood and tissues) are for total mercury and do not distinguish between inorganic and organic mercury.

The mercury content of hair can sometimes aid in estimation of body burden and may be used to trace the history of a person's exposure to methyl mercury (Kobayashi et al., 1988; Gerstner and Huff, 1977). Mercury is bound firmly to the keratin in hair, and the structure of hair is such that neither loss of mercury from hair nor contamination from external mercury sources is a significant concern (Gerstner and Huff, 1977). The fairly uniform growth rate of hair (0.75 to 1.35 cm/mo, depending on the individual) and the fact that formation of new material occurs only at one end permit estimation of approximate dates and amounts of mercury exposure. Concentrations of mercury in hair are generally 250 to 300 times higher than blood concentrations. Mean values for mercury in hair are usually in the range of 1 to 5 mg/kg, although some reported values have been as high as 25.0 mg/kg (mean for a group) and 100 mg/kg (individual sample; Gerstner and Huff, 1977). These values again are for concentrations of total mercury, both inorganic and organic.

4.3 EXCRETION

Divalent mercury can be excreted by several routes, including urine, feces (via bile, saliva, and gastric and intestinal secretions), sweat, milk, tears, and exhaled air, although most of it is removed from the body via the urine and feces (Berlin, 1986; Winship, 1985; Gerstner and Huff, 1977). Little information is available on levels of mercury in milk, tears, sweat, or expired air. Sweating has been used since at least the 18th century as a means of

lowering the body burden of mercury in cases of chronic mercury poisoning, and its use for that purpose has been suggested again in recent years (Stopford, 1979). A small amount of divalent mercury may be reduced in the body to mercury vapor, which then may be exhaled from the lungs, but this is not considered a significant route of mercury removal (Berlin, 1986; Ogata et al., 1987). The amount of mercury (Hg^0) vapor exhaled by mice following treatment with $HgCl_2$ was greater when the mice also received ethanol (Dunn et al., 1981), indicating an ethanol-sensitive reduction pathway for ionic mercury (Hg^{++}) in the body.

Mercury in the breast milk of women exposed to methyl mercury compounds was correlated with blood levels, averaging approximately 5% of simultaneous concentrations in maternal whole blood (World Health Organization, 1976). Inorganic mercury accounted for 80% of the mercury in one study and 40% in another, with the rest being methyl mercury. Suckling infants with no other mercury exposure accumulated mercury at levels in excess of 1.0 mg/L in their blood (World Health Organization, 1976).

Mercury is excreted into the intestinal tract by the liver through the bile and also by the mucous membranes of the small intestines and colon (Berlin, 1986); the latter probably involves active transport across the membranes (Gerstner and Huff, 1977). Mercury also enters the digestive tract via the saliva. Few details are known about fecal excretion of mercury. The potential for recirculation of salivary and biliary mercury must be considered, and the use of a polythiol resin to reduce resorption of mercury from the intestines has been suggested, at least for cases of methyl mercury poisoning (see Chang, 1980). Salivary mercury levels are closely correlated with mercury concentrations in blood, but not in urine, and are sometimes used to monitor occupational exposure to mercury (Stokinger, 1981; Stopford, 1979; Goldwater, 1972). Mercury was not detected in the saliva of unexposed people by a method having a sensitivity of 5 μg/L (Stokinger, 1981; Goldwater, 1972), although salivary mercury levels in workers known to have had mercury exposure ranged from 10 to 155 μg/L (Goldwater, 1972).

Most excretion of inorganic mercury occurs via the kidneys, and a greater proportion of the mercury dose is excreted in the urine than in the feces with an increase in total dose (Berlin, 1986; Chang, 1980). Approximately 60 to 75% of absorbed mercury is excreted as sulfhydryl mercury compounds, primarily with cysteine or *N*-acetylcysteine, and essentially no free inorganic mercury is found in the urine (Winship, 1985; Hultman et al., 1985).

Urinary excretion involves active tubular transport and also passive glomerular filtration (Gerstner and Huff, 1977; Berlin, 1986; Chang, 1980), although glomerular filtration is probably not a major pathway of excretion (Cherian et al., 1978). Excretion of mercury via urine is more closely correlated to blood levels than to the mercury burden of the kidney itself (Berlin, 1986).

The normal upper limit of mercury in the urine is approximately 25 to 30 μg/L (Berlin, 1986; Winship, 1985); concentrations up to 100 μg/L or more have been found in urine samples from people with no known mercury exposure, but levels above 50 μg/L are rare (Jacobs et al., 1964). In a study described by Jacobs et al. (1964) and Goldwater (1972 [this is the same study with some additional data]), 95% of urine samples had mercury concentrations less than 20 μg/L (96% were below 25 μg/L); the highest value was 221 μg/L, whereas approximately 80% contained no detectable mercury ($<$0.5 μg/L). The study included a total of 1,107 samples from 15 countries, including 434 samples from the United States. Mercury concentrations in the U.S. samples ranged from 0.0 to 221.0 μg/L, with 344 samples (79%) having mercury levels below the limit of detection. Urinary mercury excretion in children is normally less than 10 μg/L (Berlin, 1986).

Mercury levels in urine are used in monitoring exposure to mercury, although urinary concentrations vary considerably and are not always good indicators of the body burden of mercury (Winship, 1985; Gerstner and Huff, 1977). Good correlation, at least on a population level, does exist between the concentration of mercury vapor in the air and the mercury concentrations in both blood and urine (Winship, 1985; Gerstner and Huff, 1977; Jacobs et al., 1964). On an individual level, mercury levels in the urine of exposed people may fluctuate widely (as much as 3- to 10-fold) during the course of a day and from day to day (Jacobs et al., 1964). Some people with no symptoms of mercury toxicity may excrete large amounts of mercury in their urine (up to 3.0 mg Hg/L or more), whereas other people with urinary mercury levels below 0.3 mg/L may show definite signs of mercury poisoning. There seems to be no level of urinary mercury above which symptoms of poisoning may be expected and below which symptoms will not occur. There is also no evidence for a correlation between urinary mercury levels and duration of exposure to mercury, nor does there appear to be any justification for correcting urinary concentrations for the specific gravity of the sample (Jacobs et al., 1964). Urinary mercury levels in cases of acute

ingestion of mercury salts can give an indication of the amount of mercury intake, and urinary levels can also be used to monitor the effectiveness of therapeutic measures (e.g., an increased urinary mercury level would indicate that a given therapy was aiding mercury removal from the body) (Gerstner and Huff, 1977).

Because mercury levels in urine are variable, due to factors such as differences in urine flow from person to person, recent efforts have focused on normalization of mercury to urine creatinine levels. Where personal samplers have been used, the ratio between urinary mercury expressed as μg Hg/g creatinine and air ($\mu g/m^3$) has been between 1 and 2 (Figure 4-1A) (Roels et al., 1987; World Health Organization, 1991). Roels et al. (1987) reported a regression equation, where a urine mercury level of 50 μg/g creatinine (observed after exposure to 40 μg Hg/m^3) is correlated to a blood mercury level of 16 μg/L (Figure 4-1B).

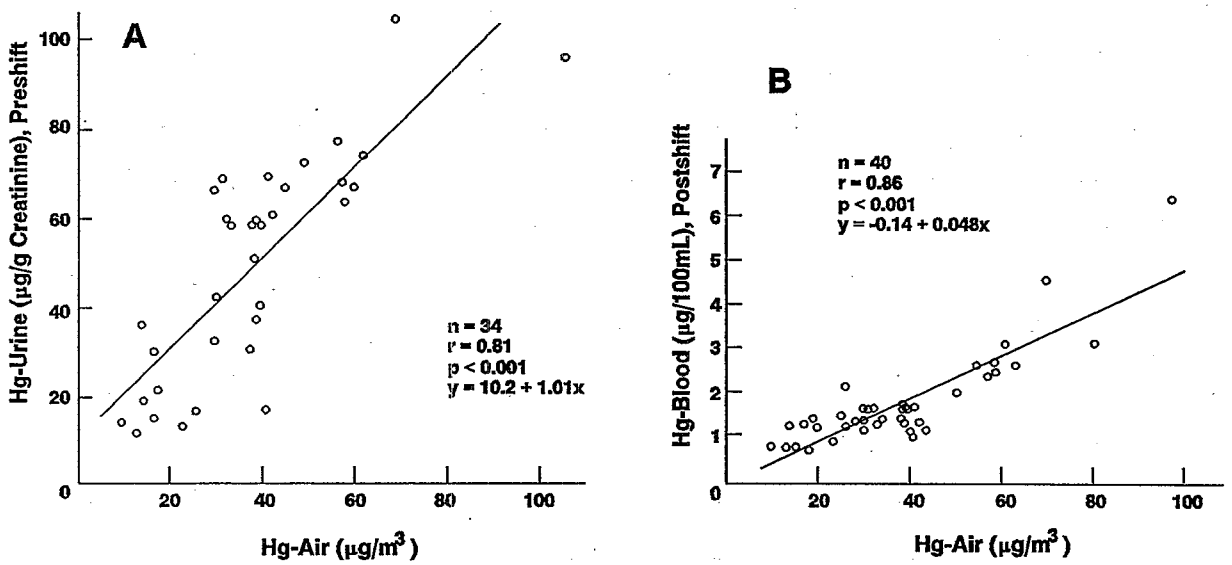

Figure 4-1. Relationships between individual daily levels of mercury in air on hopcalite filters by personal sampler and (A) those in blood samples taken at the end of the work shift (1400 hours) or (B) those in urine samples collected the following morning (0900 hours).

Source: Roels et al. (1987).

5. MUTAGENICITY AND CARCINOGENICITY

5.1 MUTAGENICITY

The genetic effects of mercury and mercury compounds have been reviewed by Leonard et al. (1983), Kazantzis and Lilly (1986), and more recently by the Agency for Toxic Substances and Disease Registry (1993). As is indicated in Tables 5-1 and 5-2, the induction of primary DNA in mammalian and bacterial cells and weak mutagenesis in mammalian cells suggest that inorganic mercury compounds have some genotoxic potential.

5.1.1 Prokaryotic Organisms

Mercury compounds have exhibited little mutagenic activity in most bacterial assay systems. Mercuric chloride failed to produce a mutagenic response in plate incorporation assays using several *Salmonella* tester strains (Wong, 1988; Arlauskas et al., 1985; Marzin and Phi, 1985). One of these experiments specifically showed that $HgCl_2$ does not cause AT $\Rightarrow$ GC base pair substitution (Marzin and Phi, 1985). Fluctuation assays in both *Escherichia coli* and *Salmonella* were also negative for $HgCl_2$-induced mutagenic activity (Arlauskas et al., 1985). Treatment of a lysogenic *E. coli* strain with $HgCl_2$ failed to induce lambda prophage, a response that would have indicated forward mutation or DNA damage sufficient for the induction of a cellular compensatory mechanism known as the "SOS" system (Rossman et al., 1984). On the other hand, Kanematsu et al. (1980) found that $HgCl_2$ did cause some DNA damage as indicated by marginal inhibition of growth in recombination-repair-deficient *Bacillus subtilis* cells at an $HgCl_2$ concentration of 1.4 mg Hg/L (0.05 M). Methyl mercuric chloride caused significantly greater inhibition of growth at a concentration of 0.14 mg Hg/L (0.005 M).

5.1.2 Eukaryotic Organisms

A major effect of mercury on the genetic material in eukaryotic systems is the inhibition of the formation of the mitotic (or meiotic) spindle, an effect known as C-mitosis (or C-meiosis) after the similar effect of colchicine (Verschaeve et al., 1985; Watanabe

TABLE 5-1. IN VITRO GENOTOXICITY OF INORGANIC MERCURY

Species (Test System)	Endpoint	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Escherichia coli	Gene mutation	–	–	Rossman et al. (1984)
Salmonella typhimurium (TA1535, TA1537, TA98, TA102, etc.)	Gene mutation	–	–	Wong (1988), Arlauskas et al. (1985), Marzin and Phi (1985)
Bacillus subtilis (H17, M45)	DNA damage	NT	+	Kanematsu et al. (1980)
Eukaryotic organisms:				
Human lymphocytes	C-mitosis	NT	+	Verschaeve et al. (1985)
Mouse lymphoma cells L5178Y	Gene mutation	(+)	–	Oberly et al. (1982)
Chinese hamster lung cells	Sister chromatid exchange	NT	–	Hsu (1979)
P388D mouse cells	Sister chromatid exchange	NT	–	Howard et al. (1991)
Chinese hamster ovary cells	Sister chromatid exchange	NT	–	Howard et al. (1991)
Human lymphocytes	Sister chromatid exchange	NT	+	Andersen et al. (1983), Morimoto et al. (1982)
Mouse embryo fibroblasts	DNA damage	NT	+	Zasukhina et al. (1983)
Rat embryo fibroblasts	DNA damage	NT	+	Zasukhina et al. (1983)
Chinese hamster ovary cells	DNA damage	NT	+	Howard et al. (1991)
Chinese hamster ovary cells	DNA damage	NT	+	Cantoni and Costa (1983)
Chinese hamster ovary cells	DNA damage	NT	+	Cantoni et al. (1982, 1984a,b)
Chinese hamster ovary cells	DNA damage	NT	+	Christie et al. (1984, 1986)
Human lymphocytes	DNA/chromosomal damage	NT	–	Umeda and Nishimura (1979), Nishimura and Umeda (1978), Paton and Allison (1972)
Human lymphocytes	DNA/chromosomal damage	NT	+	Verschaeve et al. (1985)
Chinese hamster ovary cells	Chromatin binding	NT	+	Cantoni et al. (1984a,b)

NT = Not tested.
– = Negative result.
+ = Positive result.
(+) = Weakly positive or marginal result.

TABLE 5-2. IN VIVO GENOTOXICITY OF INORGANIC MERCURY

Species (Test System)	Endpoint	Results	Reference
Somatic cells:			
Swiss mouse (bone marrow cells)	Chromosome aberrations	–	Poma et al. (1981, 1982)
Human (peripheral lymphocytes)	Structural chromosome aberrations	+	Popescu et al. (1979)
	Aneuploidy	–	
Syrian (Golden) hamsters (bone marrow cells)	Structural chromosome aberrations	+	Watanabe et al. (1982)
CFLP mice (embryonic cells)	Structural and numeric chromosome aberrations	+	Selypes et al. (1984)
Germinal cells:			
Swiss mouse (spermatogonia)	Aneuploidy	–	Poma et al. (1981)
Rat (spermatogonia)	Dominant lethal	+	Zasukhina et al. (1983), Vasil'eva et al. (1982)
Mice (spermatogonia)	Dominant lethal	–	Lee and Dixon (1975)

– = Negative result.
+ = Positive result.

et al., 1982; Galloway and Ivett, 1986). A much more gradual dose-response effect is seen with mercury compounds than with colchicine, such that at low doses of mercury the mitotic block is incomplete (Ramel, 1972); this situation can result in varying degrees of aneuploidy as well as polyploidy. The lowest dose of $HgCl_2$ that caused C-mitosis was 2.7 mg/L (Verschaeve et al., 1985). The inhibition of the mitotic spindle formation is thought to be caused by binding of the mercury to sulfhydryl groups in the proteins of the spindle fibers (Andersen et al., 1983; Leonard et al., 1983), although interaction of mercury with other proteins and enzymes such as RNA polymerase I may also be involved (Verschaeve et al., 1985).

Other reported effects of mercury compounds on the genetic material of eukaryotes include breakage of DNA; induction of point mutations, dominant lethal mutations, sister chromatid exchanges, and chromosomal aberrations; inhibition of the activity of nucleolus-organizing regions; and decreases in DNA synthesis (Howard et al., 1991; Zasukhina et al., 1983; Cantoni and Costa, 1983; Cantoni et al., 1982, 1984a,b; Christie et al., 1984, 1986; Verschaeve et al., 1983; Morimoto et al., 1982).

Verschaeve et al. (1985) found a statistically significant increase in chromosomal aberrations in human lymphocytes treated in vitro with $HgCl_2$ at concentrations as low as 1.4 mg/L (5 μM) in the culture medium, and Howard et al. (1991) reported an increase in the percentage of chromosomal aberrations in Chinese hamster ovary cells treated in vitro with 0.27 mg $HgCl_2$/L (1 μM). However, Umeda and Nishimura (1979), Nishimura and Umeda (1978), and Paton and Allison (1972) reported no increase in chromosomal aberrations in human lymphocytes or other mammalian cells treated in vitro with $HgCl_2$. Concentrations of $HgCl_2$ in the latter studies ranged from less than 8.1 μg/L (0.03 μM; Paton and Allison, 1972) to 2.7 to 17.3 mg/L (10 to 64 μM; Umeda and Nishimura, 1979; the highest dose in this study was cytotoxic).

A concentration of 3.2 mg/L $HgCl_2$ (corresponding to 50% inhibition of cell growth) did not increase the number of sister chromatid exchanges (SCEs) in Chinese hamster Don cells (derived from lung cells of a Chinese hamster named Donald; Hsu, 1979), nor did mercuric acetate or mercuric iodide at doses also corresponding to 50% cell inhibition (Ohno et al., 1982). Mercuric chloride at media concentrations up to 2.7 mg/L (10 μM) did not increase the SCE frequency in $P388D_1$ (lymphoid neoplasm-derived) mouse cells or Chinese

hamster ovary (CHO) cells (Howard et al., 1991), but did increase the frequency in some cultures of human lymphocytes (Andersen, 1983). On the other hand, Morimoto et al. (1982) found significant increases in SCE frequency in human lymphocytes treated in vitro at concentrations as low as 0.108 mg/L (0.4 μM), which was about five times the concentration of methyl mercuric chloride required to produce the same effect. Addition of sodium selenite (Na_2SeO_3), able by itself to damage DNA, to the medium at a molar ratio (selenite:mercury) of 1:1 prevented the induction of SCEs by $HgCl_2$ (a ratio of 1:2 was required to counteract methyl mercuric chloride). The mechanism of this phenomenon has not been described, but it may involve a complex of glutathione with both metals, effectively preventing damage to the DNA by either one (Morimoto et al., 1982).

Mercuric chloride in concentrations of 2.7 μg/L (10 μM) or higher also caused a decrease in the molecular weight of the DNA of intact CHO cells (Robison et al., 1982) and of nucleoids (isolated nuclear preparations) from CHO cells (Robison et al., 1984). This decrease is attributable to single-strand breaks in the DNA, rather than double-strand breaks, and it is not an artifact of the experimental techniques used (Cantoni et al., 1984a). Following treatment with $HgCl_2$, DNA-DNA cross-links, but not DNA-protein cross-links, are found (Christie et al., 1984; Cantoni and Costa, 1983); the Hg^{2+} ion binds to the DNA, replacing hydrogen in the complementary binding of thymidine to adenine (Cantoni et al., 1984b).

Mercuric chloride was mutagenic in L5178Y mouse lymphoma cells, inducing 1.4 to 3.5 times the control frequency of mutations when present in the culture medium at concentrations of 2 to 8 mg/L (Oberly et al., 1982). Metabolic activation with a rat liver S9 fraction was required to obtain the maximum response.

5.1.3 Whole Animal Assays

Male rats orally exposed daily to $HgCl_2$ (0.25 or 2.5 μg/kg body weight) for 12 mo exhibited about a fourfold increase in the frequency of dominant lethal mutations in their offspring (Zasukhina et al., 1983; Vasil'eva et al., 1982); no increase was seen at a dose of 0.025 μg/kg (2.5×10^{-5} mg/kg). No evidence of dominant lethal effects was found following treatment of male mice with 1.35 mg/kg $HgCl_2$ (1 mg Hg^{2+}/kg body weight, single intraperitoneal dose; Lee and Dixon, 1975).

Both structural and numerical chromosomal aberrations were found in the cells of mouse embryos when the mothers were exposed during pregnancy to aerosols (no mass median aerodynamic diameter given) of $HgCl_2$ (0.23 or 2.1 mg/m^3, 4 h daily for 4 days on Gestation Days 9 through 12) (Selypes et al., 1984). Chromosomal aberrations also have been reported in the peripheral blood lymphocytes of humans with occupational exposure to mercury compounds, including $HgCl_2$ (Popescu et al., 1979). The subjects of the Popescu et al. study were exposed either to mercury vapor or to mixed mercury compounds; $HgCl_2$ was a minor component of the mixture, and the observed chromosomal aberrations were not necessarily attributable to exposure to $HgCl_2$ (Popescu et al., 1979). No increased frequency of chromosomal aberrations was found in the bone marrow or spermatogonia of mice injected intraperitoneally with 2 to 6 mg/kg body weight of $HgCl_2$ (Poma et al., 1982, 1981).

The incidence of structural, but not numerical, chromosomal aberrations was slightly increased in bone marrow cells of female Syrian (golden) hamsters injected subcutaneously with $HgCl_2$ at doses of 6.4 or 12.8 mg Hg/kg body weight and examined 5 days later (Watanabe et al., 1982). Serum mercury concentrations for animals receiving the higher dose averaged 5.84 mg/L. Similar doses of methyl mercuric chloride (6.4 or 12.8 mg Hg/kg) caused some increase in numerical anomalies (particularly polyploidy) as well as structural aberrations; the average serum mercury concentration was 1.06 mg/L. Even at the higher dose of $HgCl_2$, no increase in structural or numerical aberrations was seen in metaphase II oocytes in the hamsters at either the first or second estrus following treatment. Mercury concentrations in the ovaries following the higher dose of $HgCl_2$ averaged 4.37 mg/kg at the first estrus and 6.86 mg/kg at the second. Corresponding ovarian mercury concentrations for hamsters receiving 12.8 mg/kg methyl mercuric chloride were 18.04 and 10.52 mg/kg at the first and second estrus, respectively, and some increase in numerical aberrations in metaphase II oocytes was found in these hamsters (Mailhes et al., 1986; Watanabe et al., 1982).

5.1.4 Summary

Several conclusions can be drawn from the studies described thus far. Mercuric chloride does not appear to be a potent mutagen. The mutagenic responses of eukaryotes to mercury compounds are generally less than the corresponding responses to certain other metals (e.g., cadmium or chromium) or to other known mutagenic agents (e.g., ethyl

methanesulfonate; Oberly et al., 1982), and inorganic mercury compounds usually have less of an effect than organic mercury compounds (Morimoto et al., 1982; Ramel, 1972). The occurrence of mutations (as opposed to chromosome aberrations or SCEs) may require some aspect of eukaryotic metabolism. This is suggested by the absence of increased mutations in bacterial assays (Arlauskas et al., 1985; Marzin and Phi, 1985; Rossman et al., 1984) and the requirement for a rat liver S9 fraction in the mouse lymphoma assay (Oberly et al., 1982).

In vivo studies show that low chronic doses of $HgCl_2$ can cause an increase in dominant lethal mutations in rats (Zasukhina et al., 1983; Vasil'eva et al., 1982), but much higher, single doses did not cause a similar effect in mice (Lee and Dixon, 1975). The finding in some experiments of a moderate increase in the frequency of chromosomal aberrations or SCEs indicates that $HgCl_2$ does do some damage to genetic material in vivo (Watanabe et al., 1982). Chromosomal aberrations were not found in spermatogonia or oocytes of animals receiving 4.4 (male mice) or 12.8 (female hamsters) mg Hg/kg as $HgCl_2$ (6 and 17.3 mg $HgCl_2$/kg) (Poma et al., 1981; Watanabe et al., 1982).

In the one reported experiment involving inhalation of $HgCl_2$, exposure of pregnant mice to 0.23 and 2.1 mg/m^3 resulted in genetic damage (structural and numerical chromosomal aberrations) to the embryos (Selypes et al., 1984). Although this study provides a clear indication that inhaled $HgCl_2$ can cause genetic damage and developmental effects (see Chapter 6), it did not characterize exposure adequately (e.g., particle size was not given), report the number of animals in any group, employ tests of statistical significance, or demonstrate a clear lowest-observed-adverse-effect level (LOAEL).

In vitro exposures at concentrations as low as 0.1 mg/L (Morimoto et al., 1982) also showed chromosomal effects, although other studies found no chromosomal aberrations at in vitro $HgCl_2$ concentrations as high as 17 mg/L (Umeda and Nishimura, 1979). In many of the in vitro experiments, however, cytotoxicity became a problem at or even below the concentrations of $HgCl_2$ at which chromosomal aberrations or other genetic effects were seen (e.g., Ohno et al., 1982; Umeda and Nishimura, 1979; Cantoni et al., 1984a; Kasschau and Meyn, 1981; Umeda et al., 1969). Some species or cell-type differences also may be involved in the differing responses seen. It should also be mentioned, with respect to in vitro work, that the concentration of $HgCl_2$ added to the medium is not necessarily the concentration that the cells are effectively exposed to. Other components in the medium such

as amino acids or reduced glutathione may bind Hg^{2+}, thereby making it unavailable to the cells (Cantoni et al., 1986; Costa et al., 1982; Christie et al., 1984; Verschaeve et al., 1985).

Although $HgCl_2$ is not a potent mutagen or inducer of chromosome aberrations of SCEs, some work has demonstrated that $HgCl_2$ is capable of damaging DNA and inhibiting DNA synthesis. Both in vitro and in vivo studies have shown that mercuric chloride can induce single-strand breaks in the DNA of rat- and mouse-embryo fibroblast cells; the effect is proportional to the dose, although cells from different species and strains may differ in their sensitivity to $HgCl_2$ and in their ability to repair the damage (Zasukhina et al., 1983; Vasil'eva et al., 1982).

5.2 CARCINOGENICITY

Mercuric chloride at a concentration of 13.5 mg/L (0.05 mM) enhances viral transformation in hamster embryo cells (Heck and Costa, 1982a; Casto et al., 1979), and $HgCl_2$ is weakly mutagenic in several experimental systems (see discussion in Section 5.1). Many chemicals, including some metals, are both mutagenic and carcinogenic (see Kazantzis and Lilly, 1986; Heck and Costa, 1982b); however, especially for metals, mutagenicity and carcinogenicity are not always correlated, and Heck and Costa (1982b) emphasize that each metal and even each metal compound must be considered separately. Robison et al. (1984) suggest that, in contrast to some other metal compounds such as nickel chloride, $HgCl_2$ may be too cytotoxic to be a strong carcinogen.

There are very few epidemiological studies or animal bioassays available on the potential carcinogenicity of mercury or mercury compounds (Winship, 1985; U.S. Environmental Protection Agency, 1984a,b; Andersen, 1983; Vainio and Sorsa, 1981; Shroeder and Mitchner, 1975; Fitzugh et al., 1950). The only long-term toxicity or carcinogenicity study of $HgCl_2$ is a 2-year study of F344/N rats and $B6C3F_1$ mice administered $HgCl_2$ by gavage (National Toxicology Program, 1993). Groups of 60 rats of each sex were administered 0, 2.5, or 5 mg/kg $HgCl_2$ in deionized water (dose volume 5 mL/kg) 5 days/week for 103 to 104 weeks. Groups of 60 mice of each sex were given 0,

5, or 10 mg/kg $HgCl_2$ in deionized water (dose volume 10 mL/kg) on the same schedule as the rats.

Survival was significantly ($p < 0.001$) lower after 24 mo in male rats at 2.5 and 5 mg/kg (10/50 and 5/50, respectively) than controls (26/50). During the second year of the study, body weight gains of males at 2.5 and 5 mg/kg were 91 and 85% of controls, respectively, and body weight gains of female rats at 2.5 and 5 mg/kg were 90 and 86% of controls, respectively. At study termination, nephropathy had occurred in almost all male and female rats including controls, but the number of males with severity considered to be "marked" was much greater at 2.5 and 5 mg/kg (29/50 at both doses) than in controls (6/50).

After 15 mo, the forestomach of male rats in both exposure groups developed basal cell hyperplasia, which became extensive after 2 years.. Focal papillary hyperplasia and squamous cell papillomas of the forestomach were observed in the high-dose male rats at 2 years. Squamous cell carcinomas were not observed, and it is not known if the squamous cell papillomas found had the potential to progress to carcinomas. There was no evidence that the papillomas were proceeding to malignancy. Subsequently, for male rats, the NTP reported "some evidence", rather than "clear evidence", of carcinogenic activity related to administration of $HgCl_2$. The NTP also reported an increased incidence of thyroid follicular cell adenomas and carcinomas in male rats that may have been related to $HgCl_2$ exposure. Squamous cell papillomas of the forestomach were also observed in high-dose group females. These lesions have occurred in 0/265 female historical controls at the NTP, however, because only two squamous cell papillomas were found, the data were considered to represent "equivocal evidence of carcinogenic activity" in female rats.

Survival of male mice was not affected by the administration of mercuric chloride; however, survival of high-dose females was slightly lower than controls (31/60 compared to 41/60 in controls; $p = 0.051$). Body weight gain was not affected. Female mice exhibited a significant increase in the incidence of nephropathy (21/49 in controls, 43/50 at 5 mg/kg, and 42/50 at 10 mg/kg). Nephropathy was observed in 80 to 90% of the males in all groups. Both males and females exhibited significant ($p \leq 0.001$) increases in the average severity scores for nephropathy (1.08 in control males, 1.74 in males at 5 mg/kg, and 2.51 in males at 10 mg/kg; 0.47 in control females, 1.02 in females at 5 mg/kg, and 1.24 in females at

10 mg/kg). Renal tubule hyperplasia was observed in 2/49 high-dose males compared to 1/50 controls.

Renal tubule adenomas or adenocarcinomas occurred in 3/49 high-dose male mice compared to 0/50 controls. The historical incidence of renal tubule adenomas or adenocarcinomas in males dosed by gavage was 0/205. Although the incidence of these tumors was not significantly increased, a statistically significant trend ($p = 0.032$) for increased incidence with increased dose was observed. Thus, the NTP noted equivocal evidence of carcinogenic activity in male mice based on the occurrences of two renal tubule adenomas and one renal tubule adenocarcinoma.

The NTP study of male rats provides the principle evidence for a carcinogenic effect from $HgCl_2$ exposure. However, the high mortality in male rats from severe renal disease during the last 15 weeks of the study suggests that the potential nephrotoxicity of $HgCl_2$ (see Section 7.2) may pose a greater hazard than its potential carcinogenicity (National Toxicology Program, 1993).

A 2-year feeding study in rats (20 or 24/sex/group; strain not specified) was conducted in which rats were administered mercuric acetate in the diet at doses of 0, 0.5, 2.5, 10, 40, and 160 ppm (0, 0.2, 0.1, 0.4, 1.7, and 6.9 mg Hg/kg/day) (Fitzhugh et al., 1950). Survival was not adversely affected in the study. An increase in kidney weight and renal tubular lesions was observed at 40 and 160 ppm. No effects were reported regarding carcinogenicity. However, this study was not intended as a carcinogenicity assay, the number of animals per dose was rather small, histopathological analyses were conducted on only 50% of the animals (complete histopathological analyses conducted on only 31% of the animals examined), and no quantitation of results or statistical analyses were performed.

Mercuric chloride was negative in a carcinogenicity study using white Swiss mice (Schroeder and Mitchener, 1975). Groups of mice (54/sex/group) were exposed until death to mercuric chloride in drinking water at 5 ppm Hg (0.95 mg Hg/kg/day). After dying, mice were weighed and dissected; gross tumors were detected; and some sections were made of heart, lung, liver, kidney, and spleen for microscopic examination. Mercuric chloride was nontoxic in the study. No effects were seen on the formation of tumors. This study is limited because complete histological examinations were not performed.

6. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In both humans and experimental animals, mercury and its compounds may affect development and maturation of the female reproductive system; alter the function of the hypothalamus, pituitary, or reproductive organs; decrease ovulation and implantation; decrease male fertility; and cause teratogenic effects (Lee, 1983; Mattison et al., 1983; Shepard, 1983; Koos and Longo, 1976). The effects of inorganic mercury (Hg^{2+} compounds) and organic mercury (especially methyl mercury) are different in many cases, probably reflecting both different mechanisms of action and differences in rates of absorption and clearance by specific tissues (Mueller et al., 1985; Leonard et al., 1983; Lee, 1983). In general, $HgCl_2$ is not as well absorbed, particularly following oral exposures, and causes less severe reproductive and developmental effects than does methyl mercury.

6.1 IN VITRO STUDIES

Cultured mouse embryos in the preimplantation stages were inhibited at various stages of development by 4.0 mg Hg/L $HgCl_2$ (20 μM), and mitotic arrest occurred at 10.0 mg Hg/L (50 μM) (Katayama and Matsumoto, 1985; Katayama et al., 1984; Matsumoto et al., 1984). Mercuric chloride at 1.4 mg Hg/L (5 μM) caused a decrease in protein synthesis (Katayama et al., 1984). Methyl mercuric chloride was approximately 200 times as toxic as $HgCl_2$ in terms of inhibiting embryonic cell proliferation and 20 to 50 times as toxic with respect to the inhibition of protein synthesis (Katayama et al., 1984). The difference in toxicity of the two mercury compounds was attributed to the different rates of penetration of the compounds into the embryonic cells and their different distributions within the cells (Matsumoto et al., 1984).

Mueller et al. (1985) also reported embryotoxicity of $HgCl_2$ to preimplantation mouse embryos in vitro, with 2.7 mg Hg/kg (10 μM) essentially inhibiting all growth. They also found that $HgCl_2$ enhanced the effects of x-irradiation on morphologic development and on cell proliferation. The growth of rat embryos (removed on Day 10.5 of gestation and

cultured for 48 h in vitro) was inhibited at a $HgCl_2$ concentration of 1.1 mg Hg/L (4 μM), and extreme growth retardation was observed at 2.7 mg Hg/L (10 μM) (Kitchin et al., 1984). Developmental abnormalities, primarily of the central nervous system, were observed at concentrations of $HgCl_2$ as low as 0.27 mg Hg/L (1 μM); in comparison with methyl mercuric chloride, higher concentrations of $HgCl_2$ were required to cause either abnormal embryos or embryolethality. Addition of reduced glutathione to the culture medium reduced the effects of $HgCl_2$ on the embryos (Kitchin et al., 1984).

6.2 INJECTION STUDIES

Administration of mercury salts during organogenesis can produce defects in the urogenital tract of experimental animals, probably as a result of general toxicity rather than of specific action on that system (Mattison et al., 1983). Renal effects were observed in the offspring of rats treated with a 1 mg/kg sc injection of mercuric chloride during the last 8 gestational days of pregnancy (Bernard et al., 1992). Mercury enters the hypothalamus and the anterior pituitary in animals treated with $HgCl_2$ and may have an effect there, probably on the control of ovulation (Thorlacius-Ussing et al., 1986, 1985; Mattison et al., 1983). In one study, the amount of mercury in the anterior pituitary of rats was dependent on the route and level of exposure and on the time since the last exposure (Thorlacius-Ussing et al., 1985).

Rats receiving 3 to 4 mg $HgCl_2$/kg daily by ip injection had considerably higher amounts of mercury deposited in the anterior pituitary than did rats receiving 9 mg $HgCl_2$/kg via drinking water, reflecting the low absorption rate of inorganic mercury compounds from the gastrointestinal tract. Pituitary levels of mercury declined with time after treatment, although mercury deposits were still evident 4 mo after cessation of treatment (Thorlacius-Ussing et al., 1985).

Delayed or reduced ovulation following treatment with $HgCl_2$ has been observed in Syrian hamsters receiving ip injections of 2 to 3 mg Hg/kg body weight (3 to 4 mg $HgCl_2$/kg) daily during the estrous cycle or a one-time ip injection of up to 12.8 mg Hg/kg as $HgCl_2$ (Mattison et al., 1983; Watanabe et al., 1982) and in rats receiving daily doses (by oral gavage) of 16 mg Hg/kg as $HgCl_2$ (Pritchard et al., 1982b). In the hamsters

receiving acute doses of mercury, the effect of $HgCl_2$ on ovulation was greater than the effect of an equivalent dose of methyl mercuric chloride (12.8 mg Hg/kg), although the ovarian mercury concentration was higher following treatment with methyl mercury (18.04 and 10.52 mg Hg/kg at the first and second estrus, respectively, following treatment) than following treatment with $HgCl_2$ (4.37 and 6.86 mg Hg/kg, respectively) (Watanabe et al., 1982). This difference could be attributed either to a greater toxicity to the ovaries of $HgCl_2$ than of methyl mercury or to a greater systemic effect of $HgCl_2$ (i.e., on the hypothalamus or pituitary) (Watanabe et al., 1982).

Both $HgCl_2$ and methyl mercury administered by one ip injection at a concentration of 1 mg/kg caused decreased fertility in male mice, attributed to inhibition of DNA synthesis in spermatogonial cells and possibly also to inhibition of various essential enzymes (Lee, 1983; Lee and Dixon, 1975). Mercuric chloride had a lesser antifertility effect than methyl mercury, was deposited more slowly in the testes, and was more slowly eliminated from the testes. Mercuric chloride also had its greatest effect over a different time interval posttreatment than methyl mercury, indicating different effects of the two mercury compounds on the various stages of spermatogenesis. Both compounds affected spermatogonial cells and premeiotic spermatocytes, but $HgCl_2$ did not affect early spermatids (Lee, 1983; Lee and Dixon, 1975). Inhibition of spermatogenesis may be caused by reduction of testosterone synthesis (Chowdhury et al., 1985). Recent in vivo investigations have also noted marked decreases in sperm mobility following $HgCl_2$ and methyl mercury exposure to rats (Chowdhury et al., 1989). Decreased sperm mobility has been attributed to a defect in mitochondrial energy production or a defect in chemomechanical energy transduction (Ernst et al., 1991).

Genetic or cytogenetic effects on the germ cells (e.g., chromosomal aberrations, dominant lethal mutations, aneuploidy) have not been reported in most cases following treatment of experimental mammals with $HgCl_2$ (Lee, 1983; Leonard et al., 1983; Mattison et al., 1983; Watanabe et al., 1982; Poma et al., 1981; Lee and Dixon, 1975; see discussion in Section 5.1).

Both $HgCl_2$ and methyl mercuric chloride are toxic to mouse embryos in vivo (Kajiwara and Inouye, 1986a,b, 1992). Although intravenous injections (to the mother, on Day 0 of gestation) of either compound at up to doses of 1.0 mg Hg/kg maternal body weight caused

no significant effect on embryos examined at 3.5 days gestation, the percentage of abnormal embryos was proportional to the dose of $HgCl_2$ above 1.0 mg Hg/kg, and almost 100% of the embryos were abnormal at a $HgCl_2$ dose of 2.5 mg Hg/kg (Kajiwara and Inouye, 1986a). Both mercury compounds were toxic at all stages of early embryonic development (i.e., there was no specific stage of arrest), but at later developmental stages there appeared to be some difference in response to the two chemicals (Kajiwara and Inouye, 1986b). A significant decline in body weight, corresponding to mercury dose, also was noted for the dams treated with $HgCl_2$, but not for those treated with methyl mercuric chloride. The correlation between the percentage of abnormal embryos and decrease in maternal weight suggests that embryotoxicity may be related to maternal toxicity for $HgCl_2$, and that some other mechanism may be involved in methyl mercuric chloride toxicity (Kajiwara and Inouye, 1986a).

Gale and Ferm (1971) found that mercuric acetate is embryotoxic under similar conditions. They injected pregnant golden hamsters (6 to 19 per group) intravenously with 0, 2, 3, or 4 mg mercuric acetate per kg (0, 1.3, 1.9, or 2.5 mg Hg/kg, respectively) on Gestation Day 8. Maternal animals were sacrificed on Gestation Day 12 or 14. A significantly increased incidence of resorptions was observed at all doses. In addition, increased incidences of retarded and edematous fetuses were observed at all doses (statistical significance not reported).

Gale (1974) compared the embryotoxicity of mercuric acetate in pregnant golden hamsters (3 to 23 per group) when administered by different routes. The data for oral exposure is presented in Section 6.3. Subcutaneous administration of 0, 4, 8, 20, 35, or 50 mg mercuric acetate per kg (0, 2.5, 5, 13, 22, or 32 mg Hg/kg, respectively) on Gestation Day 8 resulted in a significant decrease in the percentage of normal embryos and a significant increase in the percentage of small embryos at 4 mg mercuric acetate per kg. At 8 mg mercuric acetate per kg, significant increases in resorptions and abnormal, retarded, edematous, and malformed fetuses were observed. Intraperitoneal administration of 0, 2, 4, or 8 mg mercuric acetate (0, 1.3, 2.5, or 5 mg Hg/kg, respectively) on Gestation Day 8 resulted in significant increases in the percentage of resorptions and abnormal, small, and edematous fetuses at 2 mg mercuric acetate per kg. Intravenous administration of 0 or 4 mg mercuric acetate per kg (0 or 2.5 mg Hg/kg) on Gestation Day 8 resulted in significant

increases in resorptions and abnormal, small, retarded, edematous, and malformed fetuses at 4 mg mercuric acetate per kg. Comparison of the extent of the developmental toxicity demonstrated that the efficacy for developmental toxicity was as follows: intraperitoneal > intravenous > subcutaneous > oral.

A high rate of embryotoxicity was observed in hamsters following subcutaneous injection of pregnant females with 9.4 mg Hg/kg as mercuric acetate (15 mg/kg mercuric acetate) on Day 8 of gestation and examined on Days 12 or 15 (Gale, 1981). Adverse effects included embryonic death and both external and internal abnormalities, especially edema and cardiac abnormalities; significant variation in embryotoxicity was observed between several strains of hamsters, indicating that the genotype of an individual is important in the interaction with the teratogenic agent.

Kavlock et al. (1993) injected pregnant Sprague-Dawley rats (6 to 25 per group) subcutaneously with 0, 1, 2, 3, or 4 mg mercuric chloride per kg (0, 0.7, 1.5, 2.2, or 3.0 mg Hg/kg, respectively) on Gestation Day 7, 9, 11, or 13. On Gestation Day 21, rats were sacrificed. No increase in malformations was observed in fetuses from mercuric chloride-treated dams. Exposure on Gestation Day 7 resulted in a significant decrease in fetal weight and an increase in the number of supernumerary ribs (significance not reported) at 3 mg mercuric chloride per kg. Exposure on Gestation Day 9 resulted in significantly decreased live fetuses per litter and increased resorptions at 4 mg mercuric chloride per kg. Exposure on Gestation Day 11 or 13 resulted in no significant differences in fetal parameters.

6.3 ORAL EXPOSURE STUDIES

A group of abstracts by Pritchard et al. (1982a,b) and McAnulty et al. (1982) report on a series of investigations into the potential for oral exposures to inorganic mercury to cause reproductive and developmental effects. They reported no decrease in litter size or viability from oral doses (exposure protocol not given) of 4, 8, or 16 mg $HgCl_2$/kg administered daily from Day 15 postcoitum until Day 25 postpartum. No marked adverse effects on development or behavior of the offspring were reported, but the weight of 1-day-old offspring was reduced at 8 mg $HgCl_2$/kg/day, and subsequent weight gain of offspring in all $HgCl_2$-treated groups was reduced. Dosages up to 16 mg $HgCl_2$/kg/day were reported to have had

no adverse effects on morphogenesis, but, at 24 mg $HgCl_2$/kg/day, delayed ossification and a range of major malformations were observed in a small number (not specified) of fetuses (McAnulty et al., 1982). These results Pritchard et al. (1982b) reported no reproductive effects (i.e., effects upon fertility, conception, survival in utero) in female rats exposed (duration of exposure not specified) before mating and during gestation to as much as 12 mg $HgCl_2$/kg/day. At doses of 16 mg $HgCl_2$/kg/day and higher, they reported marked weight reduction in the dams, irregular or abolished oestrous cycles, and high preimplantation losses. An overview of these abstracts is provided as qualitative evidence of reproductive and developmental effects from $HgCl_2$ exposure. Although these data provide some indication of the low potency of inorganic mercury relative to organic mercury (McAnulty et al., 1982), they should not be relied on for a quantitative assessment due to the limited reporting of experimental detail and the lack of supportive statistics.

Gale (1974) administered 0, 4, 8, 25, 35, 50, 75, or 100 mg mercuric acetate per kg (0, 2.5, 5, 16, 22, 32, 47, or 63 mg Hg/kg, respectively) to pregnant golden hamsters (10 per dose except controls; 3 controls were used) by gavage in distilled water on Gestation Day 8. The pregnant animals were sacrificed on Gestation Day 12 or 14, and the uterine contents were examined. A statistically significant increase in the incidence of abnormal fetuses (combined incidence of small, retarded, edematous, and malformed fetuses) was observed at 25 mg mercuric acetate per kg. Statistically significant increases in the percentage of resorbed fetuses was observed at 35 mg mercuric acetate per kg and, in the percentages of small, retarded, and edematous fetuses, were observed at 50 mg mercuric acetate per kg. No treatment-related effects were observed on the fetuses at 8 mg mercuric acetate per kg.

Rizzo and Furst (1972) administered 2 mg Hg as mercuric oxide (approximately 7 mg Hg/kg) to pregnant Long-Evans rats (five per group) by gavage in peanut oil on Gestation Day 5, 12, or 19 in a pilot study. On Gestation Day 20 or 21, the rats were sacrificed, and the uterine contents were examined. Rats administered mercury on Gestation Day 5 had a higher percentage of fetuses with growth retardation and inhibition of eye formation (statistical significance not reported). Similar increases in these effects were not observed after administration on Gestation Day 12 or 19.

6.4 INHALATION EXPOSURE STUDIES

Selypes et al. (1984) reported an increase in both dominant lethal mutations and chromosomal aberrations in embryonic cells following inhalation exposure of pregnant mice to aerosols of $HgCl_2$ (0.17 and 1.6 mg Hg/m^3 [0.23 and 2.1 mg $HgCl_2/m^3$, respectively], 4 h daily during pregnancy). They also reported both decreased fetal weight and some skeletal abnormalities in offspring. However, this study was difficult to interpret because it did not characterize exposure completely (e.g., particle size was not given), report the number of animals in any group, or employ any tests of statistical significance; and it did not demonstrate a clear LOAEL.

6.5 HUMANS

There is no available epidemiological evidence concerning reproductive effects of mercury in humans (Sager et al., 1986). Only one report is available concerning potential effects of divalent mercury on human fetuses. Afonso and De Alvarez (1960; cited in Koos and Longo, 1976) describe the case of a pregnant woman who ingested 2.5 g $HgCl_2$ in an attempt to induce abortion. She developed inorganic mercury poisoning, including acute renal failure. She did abort the infant, which appeared grossly normal, but it is not clear whether the abortion was induced by the $HgCl_2$, the general toxicity of the $HgCl_2$ to the woman, or from the procedures used to treat the poisoning (Koos and Longo, 1976).
No epidemiological studies are available concerning developmental effects of $HgCl_2$ on humans, nor are any specific developmental abnormalities known to be associated with human exposure to $HgCl_2$.

6.6 SUMMARY

Several conclusions can be made from the results of the studies described thus far. Divalent mercury, and specifically $HgCl_2$, has definite adverse reproductive effects on experimental animals at certain exposure levels. Both ovulation and spermatogenesis can be delayed or reduced (Sager et al., 1986; Lee, 1983; Mattison et al., 1983; Pritchard et al., 1982b; Watanabe et al., 1982; Lee and Dixon, 1975). Mercuric chloride is toxic to embryos

of various stages both in vitro and in vivo (Kajiwara and Inouye, 1986a,b; Katayama and Matsumoto, 1985; Mueller et al., 1985; Katayama et al., 1984; Kitchin et al., 1984; Matsumoto et al., 1984; Selypes et al., 1984; McAnulty et al., 1982; Pritchard et al., 1982b; Gale, 1981). Adverse effects on embryos have been observed at in vitro $HgCl_2$ concentrations as low as 0.3 mg Hg/L (1 μM) after single in vivo intravenous injection doses to mouse dams above 1.0 mg Hg/kg (Kajiwara and Inouye, 1986a) and following repeated oral doses to rat dams above 12 mg $HgCl_2$ kg/day (Pritchard et al., 1982b). Decreased maternal weight and other signs of maternal toxicity were reported in some of the studies, as was decreased fetal or neonatal weight (Kajiwara and Inouye, 1986a; Selypes et al., 1984; McAnulty et al., 1982; Pritchard et al., 1982b; see also Magos and Webb, 1983).

Treatment by $HgCl_2$ injection during early to midgestation appeared to have a greater effect than treatment during late gestation (Pritchard et al., 1982a), although there are not yet enough available studies with which to make an adequate comparison. Two types of evidence support this idea, however. One is the finding by Kajiwara and Inouye (1986a) that mercury concentrations in the female reproductive tract decline only slightly with time after injection of the animal with $HgCl_2$, indicating that early embryos in this study were potentially exposed to mercury through the whole preimplantation period. The second type of evidence is the finding that the mercuric ion is poorly transported across the placenta (much less so than either metallic mercury or methyl mercury), but rather is concentrated in the placenta (see Ogata and Meguro, 1986; Sager et al., 1986; Khayat and Dencker, 1982; Clarkson et al., 1972). Ogata and Meguro (1986) reported ratios of mercury concentration of 0.420, 0.015, and 0.006 for placenta/maternal blood, fetus/placenta, and fetus/maternal blood, respectively, for pregnant mice injected with $HgCl_2$ on Day 18 of gestation. In other words, the placenta contained almost half the concentration of mercury that was found in maternal blood, and fetuses contained 0.6% of the maternal blood mercury concentration. Several authors report inhibition of placental transfer of nutrients by divalent mercury (e.g., Shoaf et al., 1986; Danielsson et al., 1984; Goodman et al., 1983; Miller and Holliday, 1982), and Sager et al. (1986) have suggested that mercury accumulation in the placenta compromises the development of the fetuses.

In summary, the experimental animal studies cited in this section indicate that $HgCl_2$ can affect essentially all aspects of reproduction and development. The disruption in

placental function and ensuing embryotoxicity caused by both in vivo and in vitro exposure to $HgCl_2$ provide sufficient evidence to consider this agent as a developmental toxicant in experimental animals and a likely developmental toxicant in humans. However, there is insufficient information to develop an exposure-response assessment for laboratory animals or humans for either the oral or inhalation routes of exposure.

7. OTHER TOXIC EFFECTS

7.1 ACUTE TOXICITY

Most reported cases of acute $HgCl_2$ poisoning occur by oral ingestion of the salt (Winship, 1985; Gerstner and Huff, 1977; Goldwater, 1972; Worth et al., 1984; Giunta et al., 1983; Newton et al., 1983; Stack et al., 1983; Samuels et al., 1982; Winek et al., 1981; Chugh et al., 1978), although systemic poisoning may occur from absorption through the skin (Winship, 1985; Gosselin et al., 1984). Skin contact with $HgCl_2$ may also cause skin irritation and dermatitis, and contact with the eyes may cause ulceration of the conjunctiva and cornea (Gosselin et al., 1984).

The critical organs for cases of acute ingestion of high doses of $HgCl_2$ are the gastrointestinal tract and the kidneys. The salt, or a concentrated solution of the salt, has a corrosive effect on the mucous membranes of the digestive tract (Berlin, 1986; Winship, 1985; Gosselin et al., 1984; Gerstner and Huff, 1977). Injury to the mouth, esophagus, and stomach is almost instantaneous and causes severe pain (Gosselin et al., 1984; Gerstner and Huff, 1977). The action of the salt causes extensive precipitation of proteins, and symptoms of poisoning include tissue necrosis, ashen discoloration of the exposed skin, a metallic taste, and a sense of oral and pharyngeal constriction (Berlin, 1986; Hayes, 1982; Gerstner and Huff, 1977). Vomiting usually ensues within a few minutes. If the $HgCl_2$ is permitted to reach the lower gastrointestinal tract, the result is a severe, bloody diarrhea with necrosis of the intestinal mucosa (Berlin, 1986; Winship, 1985; Hayes, 1982). In some cases, death from circulatory collapse may occur within a few hours. In patients who survive the gastrointestinal damage, renal failure generally occurs within 24 h; the major damage is necrosis of the proximal tubular epithelium, although glomerular damage may also occur (Berlin, 1986; Winship, 1985). Anuria and uremia follow, and without treatment death will occur within a few days (Berlin, 1986; Gosselin et al., 1984). Similar results will occur following poisoning with any ionizable mercuric compound; the anion seems not to be a major factor (Gerstner and Huff, 1977).

Oral doses as low as 0.5 g of $HgCl_2$ have proved fatal, although the mean lethal dose in adults is probably 1 to 4 g (Gosselin et al., 1984). The lethal concentration of mercury in

the blood is 15 mg/L (Worth et al., 1984; Winek et al., 1981), as compared with normal values of up to 10 μg/L (Gerstner and Huff, 1977; see Section 4.2). With adequate and timely treatment, patients with initial blood mercury levels as high as 1.2, 1.9, and 4.5 mg/L have recovered completely (Newton et al., 1983; Stack et al., 1983; Samuels et al., 1982). Following poisoning with mercuric salts, mercury levels in the kidney of 10 to 70 mg/kg have been reported (Berlin, 1986), in contrast to normal values of <0.1 to 3 mg/kg (see also Section 4.2). The lowest kidney mercury concentration reported for a fatal case of divalent mercury poisoning is 16 mg/kg wet weight, measured at death, 6 days after the mercury intake (Suzuki, 1979).

Acute poisoning also has been reported in surgical patients following irrigation of the wound with a solution of $HgCl_2$ (0.1 to 0.2%) in an effort to kill remaining cancer cells (Gelister et al., 1985; Laundy et al., 1984; Dick, 1983; Elliott and Dale, 1983; Lai et al., 1983). Renal failure was the major derangement noted, although circulatory collapse, vomiting, bloody diarrhea, nausea, abdominal pain, and a metallic taste in the mouth also have been reported (Laundy et al., 1984; Lai et al., 1983). Recovery often occurs, with the help of hemodialysis, but several fatalities from this treatment have been reported (see Laundy et al., 1984; Dick, 1983). Other chemicals are available that are at least as effective as $HgCl_2$ in destroying stray cancer cells (Umpleby and Williamson, 1984), and it has been suggested that $HgCl_2$ should no longer be used for this purpose because of the high risk of renal failure and death (Gelister et al., 1985; Laundy et al., 1984; Dick, 1983; Elliott and Dale, 1983; Lai et al., 1983).

The kidneys of newborn and suckling rats are less sensitive to inorganic mercury toxicity than are the kidneys of adult rats, possibly because a smaller proportion of the dose reaches the kidneys in the young animals (Daston et al., 1983, 1984, 1986; Jugo, 1979). The difference in toxicity with age ultimately may be caused by differences in metallothionein levels (see Section 4.2). Mercuric chloride was administered by subcutaneous injection in these experiments. For young animals ingesting $HgCl_2$ orally, the decreased sensitivity may be offset somewhat by a greater gastrointestinal absorption of mercury (see Section 4.1). No comparable data are available concerning acute nephrotoxicity of $HgCl_2$ in newborn humans.

Despite much laboratory research, the pathogenesis of acute renal failure is not well understood. Studies in rats injected once with 3.5 mg $HgCl_2$/kg suggest that tubular obstruction and back-leak of tubular fluid is the primary pathogenic mechanism in $HgCl_2$-induced acute renal failure and that hemodynamic factors such as a decrease in the glomerular permeability coefficient may be secondary (Conger and Falk, 1986). However, the relative contributions of these various factors during the different phases of acute renal failure is a matter of considerable controversy. Contrary to some theories, the renin-angiotensin system does not seem to be an important factor (Conger and Falk, 1986; Daston et al., 1983; De Rougemont et al., 1982), and, despite some pharmacologic evidence that adenosine mediates the observed hemodynamic changes, a recent bioassay to delineate the role of renal adenosine system in $HgCl_2$-induced renal failure provides no support for this hypothesis (Rossi et al., 1990). The underlying mechanisms may involve effects of Hg^{2+} on essential enzymes, membrane transport processes, and mitochondrial function resulting in necrosis of cells, particularly in the proximal tubular region (see for instance Ansari et al., 1990, 1991; Rossi et al., 1990; Bulger, 1986; Nicholson et al., 1985; Schwertz et al., 1985; Weinberg et al., 1982a,b; Trifillis et al., 1981). In vitro exposure of human erythrocyte to $HgCl_2$ causes a considerable decline in glutathione content (Bansal et al., 1992), and glutathione depletion markedly alters the effects of $HgCl_2$ on rat renal function (Ansari et al., 1991; Guillermina et al., 1989). Mercuric chloride also enhances the rate of superoxide dismutation, leading to increased production of hydrogen peroxide (H_2O_2), which may contribute to its oxidative tissue damaging properties (Miller et al., 1991; Woods et al., 1990a,b). Recent findings suggest that cytosolic calcium (Ca^{2+}) deregulation may play a role in $HgCl_2$ toxicity (Smith et al., 1991).

7.2 SUBCHRONIC AND CHRONIC TOXICITY

7.2.1 Health Effects

Chronic exposure to mercuric compounds such as $HgCl_2$ without concurrent exposure to metallic mercury vapor is considered rare (Berlin, 1986). Chronic exposure to calomel (mercurous chloride) or to mercury-containing skin ointments also is found (Dyall-Smith and Scurry, 1990; Berlin, 1986; Winship, 1985).

The major effect of chronic exposure to low levels of divalent mercury is kidney damage; other symptoms in humans may include increased salivation, inflammation in the gums, and black lines on the teeth (World Health Organization, 1991; Berlin, 1986). Renal damage from chronic exposure to $HgCl_2$ administered by gavage, subcutaneously or intramuscularly has been observed in experimental work with mice, rats, and rabbits (Dieter et al., 1992; National Toxicology Program, 1993; Andres and Brentjens, 1984; Enestrom and Hultman, 1984; Madsen and Maunsbach, 1981). Bernaudin et al. (1981) identified similar renal damage following repeated mercuric chloride intratracheal and aerosol exposures to rats (see Section 8.6). Two types of renal damage have been observed in animals and humans: (1) glomerular injury caused by an autoimmune reaction against the glomerular tissue, and (2) tubular damage caused by necrosis in the proximal tubule (World Health Organization, 1991; Berlin, 1986). Immune responses to inorganic mercury also are involved in erythema and contact dermatitis following application of mercury compounds to the skin (Berlin, 1986; Stokinger, 1981). Similar immune responses were also noted in the lungs and spleens of rats intratracheally exposed to mercuric chloride (Bernandin et al., 1981).

Children between 4 mo and 4 years of age may develop a syndrome known as acrodynia or pink disease following chronic exposure to low levels of any of a number of mercurial compounds (Berlin, 1986; Bilderback and Anderson, 1975). This disease is characterized by generalized body rash, pink coloring of the extremities, listlessness and irritability, excessive perspiration and thirst, depressed appetite, and severe pain (Gosselin et al., 1984; Bilderback and Anderson, 1975). Increased levels of mercury (usually >50 μg/L) are found in the urine. Acrodynia is thought to be a special form of mercury hypersensitivity, as only a fraction of chronically exposed children (perhaps 1 in 500) develop the disease (Berlin, 1986; Winship, 1985; Bilderback and Anderson, 1975).

Mercury is a potent neurotoxin, and chronic exposure to methyl mercury compounds or metallic mercury vapor in particular can cause severe damage to the human central nervous system. Divalent mercury does not as readily pass the blood-brain barrier (see Section 4.2), and its major effect in humans is on the kidneys. Ultrastructural alterations of brain cortex have been observed in rats following intraperitoneal administration of a single dose (6 mg/kg body weight) of mercuric chloride (Gajkowska et al., 1992). Behavioral effects have been reported in animals following exposure to divalent mercury (Evans et al., 1975); neurological

effects due to divalent mercury alone are probably possible in humans as well, but are likely to be of less importance than renal effects. Chronic $HgCl_2$ exposure in animals has also been associated with systemic toxicity, poor appetite, decreased respiratory function, cardiovascular effects, endocrinopathy, and skin conditions (National Toxicology Program, 1993; Agrawal and Chansouria, 1989; Carmignani et al., 1983; McAnulty et al., 1982; Pritchard et al., 1982b; Roberts et al., 1982).

7.2.2 Pathology of Immunological Effects

During the last two decades, great attention has been paid to effects of inorganic mercury on the immune system. The most sensitive adverse effect caused by mercuric mercury is the formation of mercuric-mercury-induced autoimmune glomerulonephritis, particularly in the Brown Norway strain of rats. However, it is important to note that in at least one other strain (Lewis rats) immunosuppression is observed (World Health Organization, 1991). An autoimmunological origin of glomerular nephritis following mercury exposure is well documented, however, in the Brown Norway strain of rat (Andres, 1984; Fukatsu et al., 1987; Knoflach et al., 1986; Druet et al., 1982a; Bernaudin et al., 1981) and can occur at doses too low to cause toxic lesions such as renal tubular necrosis (Knoflach et al., 1986). Brown Norway rats injected with low intravenous doses of $HgCl_2$ have been shown to develop a variety of autoimmune abnormalities, including lymphoreticular proliferation as indicated by spleen and lymph node enlargement, increased production of nonspecific IgE, and development of circulating antibodies to the glomerular basement membrane (Dubey et al., 1993; Esnault et al., 1992; Druet et al., 1978, 1982a). Autoimmune disease of the kidney has been reported in the Brown Norway rat following sc injection of 150 μg $HgCl_2$/kg/week (Druet et al., 1978), gavage administration of 1,500 μg $HgCl_2$/kg/week (Knoflach et al., 1986) and 3,000 μg $HgCl_2$/kg/week (Bernaudin et al., 1981), intratracheal installation of 110 to 750 μg $HgCl_2$/kg/week (Bernaudin et al., 1981), or inhalation of an aerosol air concentration estimated at 1 mg $HgCl_2/m^3$ (see Chapters 1 and 8) for 1 h/day, 4 days/week for 2 mo (reported lung retention was 50 to 60 μg $HgCl_2$/kg/h). No immunologic response to the kidney was seen following intratracheal installation of 60 μg $HgCl_2$/kg/week (Bernandin et al., 1981).

This autoimmune response is not observed in other inbred strains of rats, indicating that a genetic component is involved in susceptibility (Druet et al., 1982b). Several genes appear to be involved, including genes linked to the histocompatibility complex (Druet et al., 1982b; Sapin et al., 1982); however, the specifics of genetic control of $HgCl_2$-induced autoimmunity appears to be quite different between the animal species and strains (Saegusa et al. 1991). The genotype of the host immune system seems to be more important than the genotype of the kidney (Druet et al., 1983).

This autoimmune disease is characterized by the production of autoantibodies to renal and extrarenal basement membranes. These antibodies are found deposited along the glomerular basement membrane in a linear pattern. After 3 to 4 weeks, a typical membranous glomerulopathy with granular, subepithelial immunoglobulin G (IgG) deposits is observed. The majority of rats develop proteinuria, which progresses in some animals to nephrotic syndrome (World Health Organization, 1991). The disease is transient, and rats that do not die recover. The fine mechanism of action at the cellular level remains to be fully elucidated. It is known that mercuric chloride induces a polyclonal activation of B cells in Brown Norway rats (Pelletier et al., 1988a). T cells are required for this activation, as Brown Norway rats depleted of T cells are resistant (Pelletier et al., 1987a). T cells from Brown Norway rats injected with mercuric chloride are able to transfer autoimmune manifestations to normal Brown Norway recipients and Brown Norway rats depleted of T cells (Pelletier et al., 1988b).

Different effects of $HgCl_2$ on the immune system have been observed in other rat strains and in mice. Decreased hemolytic complement activity has been observed in intravenously exposed Wister rats (Asahara and Mochizuki, 1981). Induction of antinuclear antibodies has been described in several other strains of rats and mice (Goter Robinson et al., 1984, 1986; Hultman and Eneström, 1992; Kubicka-Muranyi et al., 1993). In sharp contrast to Brown Norway rats, Lewis rats are genetically resistant to induction of autoimmunity via injection of $HgCl_2$. For this reason, $HgCl_2$-induced immune dysregulation in the rat is being used as a model to study the effects of an immunotoxic agent on different target cells (Dubey et al., 1993; Pelletier et al., 1987b). Recent studies have demonstrated a dose-related decrease in human lymphocyte (T and B cell) and monocyte viability and function (Shenker et al., 1992a,b, 1993a).

7.3 BIOCHEMICAL EFFECTS

Investigators have known for many years that the mercuric ion interacts readily with sulfhydryl (SH) groups both on proteins and on small molecules such as glutathione (MacGregor and Clarkson, 1974). Recent studies, however, provide evidence that the impact of mercury on GSH levels may play an important role in the aforementioned cytotoxicity associated with low-level mercury exposure (Shenker et al., 1993b; van der Meide et al., 1993). Shenker et al. (1992a,b) found that mercury inhibited in vitro activation of T-cells only in the presence of monocytes, and that, of the cells they examined, monocytes were the most sensitive to the cytotoxic effects of mercury. Because monocytes are known to play a role in regulating lymphocyte GSH levels, these investigators also determined the relation between this mercury-induced cytotoxicity and GSH levels (Shenker et al., 1993b). They found that sensitivity of human lymphocytes to the toxic effects of mercury is related to the endogenous levels of GSH. They also determined that, at low concentrations, mercury decreases the GSH concentration of lymphocytes and monocytes. Thus, because GSH provides the major source of reducing equivalents in the cell, a decrease in the level of this intermediate and subsequent alterations in the thiol redox could, at least in part, account for the aforementioned cellular changes associated with low-level mercury exposure.

Mercury also may form complexes with various other ligands in biological systems, including the nitrogen bases of DNA (Cantoni et al., 1984b; see Section 5.1). The specific ligand (SH or non-SH) that combines with the mercuric ion is highly dependent on the biological situation, including such factors as the ability of the mercuric ion to reach a certain intracellular site and the availability and accessibility of specific ligand sites (MacGregor and Clarkson, 1974). Many of the physiological effects of mercury probably are attributable to the effects of its binding to and subsequent altering of various macromolecules, including but not limited to SH-containing enzymes.

Mercuric chloride has been shown to inhibit a number of enzymes either in vitro or in vivo, including (but not limited to) lactate dehydrogenase, glutamic-oxaloacetic transferase, carbonic anhydrase, adenosine triphosphatase, acetylcholinesterase, ribonuclease, lipase, thyroid peroxidase, urease, hexokinase, alkaline phosphatase, glucose-6-phosphatase, and Na^+/K^+-ATPase (Nishida et al., 1990; Magour et al., 1987; Magour, 1986; Mehra and Kanwar, 1986; Lai and Barrow, 1984; Christensen et al., 1982). Other enzymes, such as

acid phosphatase or alkaline phosphatase in certain tissues (Mehra and Kanwar, 1986) and renal UDP glucuronyl transferase (Tan et al., 1990) may be induced by $HgCl_2$. Inhibition or induction of enzymes in vivo is tissue and enzyme specific, and may vary with the duration of exposure, level of maturity or sex of the individual (Dieter et al., 1992; Mehra and Kanwar, 1986; Bartolome et al., 1984). For example, urinary levels of alkaline phosphatase and gamma-glutamyl transferase were higher in both male and female rats at 4 mo, higher only in female rats at 6 mo, and no different from controls in either sex after 2 years of gavage exposures (5 days/week) to $HgCl_2$ (Dieter et al., 1992).

Mercuric chloride induces biosynthesis of metallothionein in experimental animals, especially in the kidneys, and the binding of the mercuric ion to metallothionein is involved in the accumulation of mercury in the kidney (Berlin, 1986; Chmielnicka et al., 1983; Piotrowski et al., 1974). Urinary metallothionein levels also increase following exposure to mercury (Lee et al., 1983). The increase in kidney metallothionein does not occur in the presence of selenium (Chmielnicka et al., 1986); selenium appears to have an antagonistic effect on the acute toxicity of $HgCl_2$, diminishing the affinity of Hg for the kidney and increasing the whole-body retention of mercury (Christensen et al., 1991; Chmielnicka et al., 1986). Other metals such as zinc, tellurium, and copper also may be involved in the metabolism of Hg or Hg^{2+} in the mammalian body, and vice versa (e.g., Chmielnicka et al., 1983, 1986; Fukino et al., 1986; Khayat and Dencker, 1984). Muto et al. (1991) observed increased copper levels in the livers and kidneys of rats 24 h after injection with 1 mg $HgCl_2$/kg. Selenium, zinc, and tellurium seem to decrease the toxicity of inorganic mercury, possibly by mechanisms involving glutathione complexes (see Fukino et al., 1986; Morimoto et al., 1982; Naganuma et al., 1982).

Other biochemical effects of $HgCl_2$ include inhibition of the polymerization of microtubules (De Saint-Georges et al., 1984), altered release of neurotransmitter substances (McKay et al., 1986a,b), changes in calcium homeostasis (McKay et al., 1986b; Shier and DuBourdieu, 1983), induction of phospholipid hydrolysis and prostaglandin synthesis (Shier and DuBourdieu, 1983), inhibition of vasopressin release (Clifton et al. 1986), inhibition of glucose metabolizing enzymes (Dieter et al., 1983), initiation of peroxidation in erythrocytes (Ribarov et al., 1983, 1984), and alterations in the complement system (Asahara and Mochizuki, 1981). Mercuric chloride also causes structural and functional damage to

biological membranes, resulting in altered permeability of cells at an in vitro exposure concentration of 10^{-5} M (Walum and Marchner, 1983) or altered mitochondrial function in rats as a result of subcutaneous injection of 5 mg $HgCl_2$/kg (Weinberg et al., 1982a,b). In short, a large number of cellular and subcellular systems or functions are adversely affected by the presence of $HgCl_2$ or the mercuric ion. Many of the pathogenic effects of $HgCl_2$ probably occur as a result of general disruption of cellular metabolism causing general toxicity to cells, tissues, or entire organisms (see Section 5.1 and Chapter 6).

8. U.S. ENVIRONMENTAL PROTECTION AGENCY CANCER AND NONCANCER ASSESSMENTS

8.1 CARCINOGENICITY

On January 13, 1988, EPA's Carcinogen Risk Assessment Verification Exercise (CRAVE) Work Group assigned inorganic mercury a "D" classification ("not classifiable as to human carcinogenicity"). The results of a chronic, gavage exposure carcinogenicity study recently were finalized by NTP (National Toxicology Program, 1993). On March 3, 1994, EPA's CRAVE Work Group reassigned inorganic mercury a "C" classification, which means that inorganic mercury is a "possible human carcinogen". This reclassification should be considered preliminary until it is officially posted on the EPA Integrated Risk Information System (IRIS) database. It is based on evidence of carcinogenicity in rats and mice following gavage exposures (National Toxicology Program, 1993) (see Section 5.2). No human data are available. No quantitative cancer risk assessment has been performed for inorganic mercury.

8.2 DRINKING WATER EQUIVALENT LEVEL

On October, 26 and 27, 1987, a panel of mercury experts met at a Peer Review Workshop on mercury issues in Cincinnati, OH, and reviewed outstanding issues concerning the health effects and dose-response assessment of inorganic mercury (U.S. Environmental Protection Agency, 1988a). Drinking Water Equivalent Level (DWEL) values were derived for several individual studies, including Druet et al. (1978). In this study, Brown-Norway rats were exposed to mercuric chloride via subcutaneous injection, 3 times/week for 8 weeks. The dose levels were 0, 100, 250, 500, 1,000, and 2,000 μg/kg, and there were 6 to 20 animals/groups. An additional group of animals received 50 μg/kg for 12 weeks. Proteinuria occurred at doses $\geq$100 μg/kg (LOAEL); the proteinuria was considered a highly deleterious effect, as if frequently let to hypoalbuminemia and even death. A DWEL of 7.0 μg/L was calcuated.

In a 60-day study conducted by Bernaudin et al. (1981), Brown-Norway rats (5/dose groups) were force-fed 0 or 3,000 μg/kg/week mercuric chloride. At the end of the 60 days, there were no histological abnormalities in the kidneys of treated animals. Using immunofluorescence, however, IgG deposition was evidence in all of the treated rats, and weak proteinuria was noted in 3/5 dosed animals. Based on the LOAEL of 3,000 μg/kg/week, the EPA derived a DWEL of 11 μg/L. Similar results were obtained by Andres and Brentjens (1984). Brown-Norway rats were exposed to 3,000 μg/kg mercuric chloride via gavage 2 times/week for 60 days. After 60 days, the kidneys of all treated animals appeared normal histologically and there no proteinuria was reported in any treated animals, but IgG deposition in the renal glomeruli was demonstrated using immunofluorescence in Brown-Norway rats. Based on the LOAEL of 3,000 μg/kg, a DWEL of 22 μg/L was deterimed.

Some of the consensus conclusions and recommendations that resulted from this workshop are presented below.

- The most sensitive adverse effect for mercury risk assessment is formation of mercuric-mercury-induced autoimmune glomerulonephritis. The production and deposition of immunoglobulin G (IgG) antibodies to the glomerular basement membrane can be considered the first step in the formation of this mercuric-mercury-induced autoimmune glomerulonephritis.

- The Brown Norway rat should be used for mercury risk assessment. The Brown Norway rat is a good test species for the study of autoimmune glomerulonephritis. The Brown Norway rat is not unique in this regard (this effect has also been observed in rabbits).

- The Brown Norway rat is a good surrogate for the study of mercury-induced kidney change in sensitive humans. For this reason, the uncertainty factor used to calculate criteria and health advisories (based on risk assessments using the Brown Norway rat) should be reduced by 10-fold.

- A drinking water equivalent level (DWEL) of 0.010 mg/L was recommended based on the weight of evidence from the studies using Brown Norway rats and limited human tissue data.

Thus, three studies using the Brown Norway rat as the test strain, Druet et al. (1978), Bernaudin et al. (1981), and Andres and Brentjens (1984), were chosen from a larger

selection of studies as the basis for the panel's recommendation of 0.010 mg/L as the DWEL for inorganic mercury (U.S. Environmental Protection Agency, 1988a).

8.3 MAXIMUM CONTAMINANT LEVEL GOAL

The EPA promulgated a maximum contaminant level goal (MCLG) of 0.002 mg/L (Federal Register, 1991) based upon this DWEL and an assumed drinking water contribution of 20% (i.e., the MCLG assumes that drinking water exposure accounts for just 20% of an individual's total exposure to inorganic mercury).

8.4 MAXIMUM CONTAMINANT LEVEL

The maximum contaminant level (MCL) is equal to the MCLG of 0.002 mg/L. Ground water systems must be monitored every 3 years and surface water systems must be monitored annually to ensure compliance with the MCL.

8.5 ORAL REFERENCE DOSE

An oral Reference Dose for chronic oral exposure (RfD) of 3 E-4 mg/kg/day has been determined by the EPA, based on autoimmune glomerulonephritis observed in rats. The RfD was back-calculated from the 0.01 mg/L DWEL discussed previously.

8.6 INHALATION REFERENCE CONCENTRATION

Only two studies on the health effects of inhaled mercuric chloride are available, one investigating autoimmune disease in rats (Bernaudin et al., 1981) and the other genotoxicity and developmental effects in mice (Selypes et al., 1984).

Bernaudin et al. (1981) exposed Brown Norway rats (male and female, number per gender not specified) to aerosols of mercuric chloride for 4 h/week for 2 mo. The exposure was not well characterized (i.e., no mass median aerodynamic diameter or sigma g provided,

and the particle generation system was not adequately described). The authors calculated a retained amount of 5 to 6 μg $HgCl_2$/h/100 g of body weight based on radiolabeled mercury.

During immunomorphological studies of the pattern of fixation of fluoresceinated sheep anti-rat IgG conjugates to kidney biopsies during the exposure period (Day 15) and to kidney, lung, and spleen tissue from sacrificed animals at the conclusion of the exposure period (Day 60), the following were observed: linear pattern of fixation in kidney glomeruli for five of five rats at Day 15 and granular pattern of fixation in kidney glomeruli and arteries, lung, and spleen for three of three rats at Day 60. The difference in the number of animals for which observations were made at the conclusion of the exposure period (i.e., three rather than five) was not explained. In two of three rats exposed to aerosols and examined when sacrificed, weak proteinurea (1, 28, and 47 mg/day) was detected. Data for 22 control rats (10 administered acidic water, 10 injected subcutaneously, 7 exposed to aerosol, and 5 force-fed) were presented together with no report on statistical analysis. No fixation of IgG conjugate was observed in any of the control animals.

Selypes et al. (1984) exposed an unspecified number of female CFLP mice to an uncharacterized aerosol of 2.1 or 0.23 mg/m^3 for 4 h on 4 days during pregnancy (Days 9 to 12). A "significant" increase in dead embryos and postimplantation dominant lethals at both concentrations was reported. Values are provided for controls, but no statistical analysis is mentioned. A "significant" increase in the number of embryos with bone aberrations (retardation symptoms described as similar to those caused by lead) was also reported at both concentrations, but no changes indicating teratogenic effects were found based on "investigation of the inner organs." Significantly increased numbers of embryonic cells with chromosomal aberrations (most frequently deletions) were reported.

No information is available on the health effects of inhaled mercuric chloride in humans. Information on health effects from oral exposures is principally from accidental or intentional acute oral exposures. These ingestions can be fatal and often involve corrosive effects on the gastrointestinal tract and occasionally renal failure (Troen et al., 1951).

Due to the limitations of the available inhalation studies and the inadequacy of the toxicologic and pharmacokinetic data bases, the EPA RfD/RfC Work Group determined that derivation of an RfC is not possible. The posting of this determination on the EPA IRIS database is proceeding concurrent with the finalization of this document.

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