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Mercury and Dimethylmercury: Exposure and Effects

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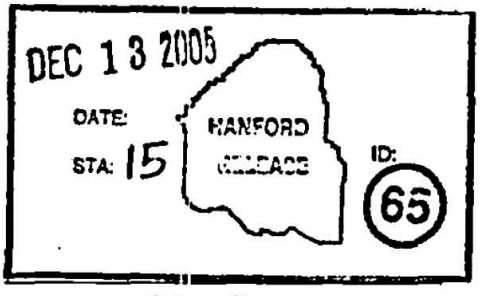
Abstract:
This report identifies the dose response data available for several toxic mercury compounds and summarizes the symptoms and health effects associated with each of them.



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MERCURY AND DIMETHYLMERCURY: EXPOSURE AND EFFECTS

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FOREWORD

This document was researched and developed by Dr. Michael Gochfeld, Rutgers University in late 2004 and originally submitted as a review draft in December, 2004. Final editing and some additional occupational exposure information was added by CH2MHILL Hanford Group, Inc. to capture this information for use in developing appropriate Industrial Hygiene control measures once workplace sampling is completed, and actual dimethylmercury concentrations in the workplace are determined.

This report is a survey of the published literature regarding organic mercury compounds and the available epidemiological and toxicological information. It does not provide new or modified occupational exposure limits, other than those established by NIOSH, OSHA, and AGCIH.

EXECUTIVE SUMMARY

All mercury compounds are toxic, and many have been used specifically for their ability to kill algae, fungi, and bacteria. Organic mercurial compounds have higher toxicity than elemental mercury which in turn is more toxic than most of the inorganic mercury compounds. They also have high bioavailability and undergo food chain bioamplification. Among the organomercurials, dimethylmercury (DMHg) is probably the most dangerous (based on the fatal case of Dr. Wetterhahn at Dartmouth College attributed to a few drops of the compound absorbed dermally). It is also the least known of the organomercurials; most attention has focused on the widespread and also highly toxic methylmercury (MeHg) compounds.

This report was undertaken to identify dose-response data that would be useful for industrial hygiene. Such data are quite limited for MeHg and essentially unavailable for DMHg.

Organic mercury compounds are readily absorbed through the skin, intestine, and lungs. They bind readily to the sulfur on proteins including enzymes which accounts for much of the damage they cause. The alkylmercury compounds methyl, dimethyl, and ethylmercury are slowly converted to inorganic mercury. Organic mercurials are excreted mainly via the bile and feces, but are also readily deposited in hair and nails. Inorganic mercury is mainly excreted in the urine, and contributes only a small amount to the mercury in hair.

Poisoning due to MeHg and DMHg results in nervous system symptoms after a period of weeks or months. This long latency poses a serious challenge for industrial hygiene and occupational medicine. Often symptoms do not appear until exposure has terminated, hence exposure is usually quantified retrospectively. The concentration in hair has proven useful as a way of estimating individual exposure periods and amounts, albeit with some uncertainty.

Two other historical events involved deaths attributed to DMHg production (1865, 1971), while there are now hundreds of deaths attributed to MeHg.

There is a fairly consistent spectrum of health effects that is apparent when the single DMHg (1996-1997) laboratory fatality is compared with the larger published series of cases from a MeHg poisoning episode in Iraq (1971-1972). However, the laboratory fatality had a blood mercury level of 2,000 µg/L when first discovered so provides little information on low-level effects.

Since it is believed that DMHg is converted to MeHg in the body before entering the brain, the sequence of neurotoxic events should be similar for the two substances.

The first symptom usually reported with MeHg is tingling in the lips and fingertips (paresthesias). In the Iraq epidemic, paresthesias occurred in people with levels below 100 µg/L blood mercury level. But the lowest level at which paresthesias occurred was not documented.

The second symptom is some form of motor-incoordination. In fish-eaters, clumsiness in the hands and fingers is an early finding, but in the Iraq epidemic this was not reported, rather, ataxia

or clumsy stumbling gait was noted, in some people with blood mercury levels below 100 µg/L, and in 100% of those who exceeded 3,000 µg/L.

The third symptom to occur is usually some report of visual changes such as narrowed visual fields or flashing lights. In Iraq this occurred at blood mercury levels above 500 µg/L.

Dysarthria or difficulty forming clear speech occurred in Iraqi subjects who exceeded a blood mercury level of 1,000 µg/L, and deafness ensued in a few people above 2,000 µg/L. The threshold for death was 3,000 µg/L.

What is lacking from the Iraq data is information on the low-level exposures and effects that would have occurred at blood mercury levels of 20 µg/L (usually considered the upper limit of "normal") or 50 µg/L at which other researchers have reported subtle neurobehavioral effects.

The laboratory death from DMHg poisoning presumably involved liquid contact with skin, although there was the potential for inhalation of this highly volatile compound.

The National Institute of Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (AGCIH), and the Occupational Safety and Health Administration (OSHA) all have established an time weighted average concentration limit for alkyl mercuric compounds at 0.01 mg/m^3 as mercury for methyl, dimethyl, and diethyl mercury compounds. They also indicate that skin protection is required. Since dimethylmercury has been demonstrated to quickly penetrate latex gloves, gloves impervious to chemical absorbtion (such as SilverShield TM) must be used whenever significant dimethylmercury concentrations are detected in workplace breathing zones or in aqueous or organic condensates.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TERMS

Abbreviations and Acronyms

DMHg	dimethylmercury
MeHg	monomethylmercury
MSDS	Material Safety Data Sheet
NMR	Nuclear Magnetic Resonance

Units

cm	centimeters
cm^3	cubic centimeters
°C	degrees Celsius
g	grams
kg	kilograms
L	liter(s)
m	meters
m^3	cubic meters
mg	milligrams
mL	milliliters
mm	millimeters
ppb	parts per billion
ppm	parts per million
sec	seconds
µg	micrograms

1.0 BACKGROUND

Mercury is a heavy metal (average Molecular Weight = 200) that has been exploited for its unique properties for over 2,000 years. It is one of the few metals that is liquid at ambient temperature. It can exist in elemental form (quicksilver), as an ion in inorganic "salts," and in a variety of organic compounds, among which dimethylmercury (DMHg) is the most dangerous. Elemental mercury forms amalgams with other metals, including gold, and is still used in gold mining operations in many parts of the world. Silver amalgams continue to be used in dentistry, which remains as a significant public health controversy. Mercury has been important in industrial chemistry, as a catalyst, in instruments, electronics, pharmacy, and pigment manufacture. Mercury is universally toxic to living organisms, hence its widespread use as an antiseptic (mercurochrome), preservative (thiomersal), and pesticide (various organomercurial anti-fungal seed dressings).

In the developed nations, exposure to mercury from industrial and agricultural sources has been greatly reduced over the past 30 years. While developing nations continue to grapple with industrial mercury contamination, most attention in North America has focused on the inadvertent release of mercury from coal during electric generation, and its subsequent atmospheric transport, deposition, and accumulation in aquatic ecosystems, resulting in potential human exposure from consuming fish. The balance between beneficial effects of eating fish and harmful effects of contaminants is a topic of controversy (National Research Council 2000). Also controversial is the role of dental amalgams and thiomersal in vaccines as a cause of disease (Clarkson 2002).

2.0 FORMS OF MERCURY

Mercury occurs in three major forms or classes: elemental (Hg^{o}), inorganic or ionic (Hg^{+}, Hg^{++}), and organic. Within the latter two classes, individual compounds (methylmercury, ethylmercury, etc.) are referred to as "species," a confusing term when its distribution in biological species (fish, birds, etc.) is being considered. Dimethylmercury is one of the least known of these compounds (see Table 1). This review was undertaken utilizing the National Library of Congress MEDLINE, accessed through a universally free portal PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). Since the entries are accessed by keywords which may have multiple meanings, the number of entries exceeds the actual number of relevant papers. This is particularly common in GOOGLE searches. Thus, the keyword "mercury" would elicit entries on the planet, automobile, and newspapers named "Mercury" as well as on all chemical entries containing the keyword "Mercury" but not entries with only the word "Mercurial." Table 1 highlights the paucity of information on DMHg relative to other forms of mercury in both MEDLINE and GOOGLE.

Table 1. Number of Scientific Paper Entries

(Identified through PUBMED from the National Library of Congress MEDLINE database of biomedical scientific papers and number of GOOGLE entries (December 20, 2004) for comparison of relative knowledge base for mercurial compounds © EOHSI.)

SEARCH TERM	PUBMED	GOOGLE
Mercury	23,351	24,600,000
Elemental mercury	425	42,800
Inorganic mercury	1,282	34,600
Organic mercury.	1,164	23,200
Mercurous	46	17,600
Calomel	268	65,900
Mercuric	3,790	153,000
Methylmercury	3,219	135,000
Ethylmercury	380	9,010
Thimerosal (also spelled thiomersal)	1,021	218,000
Phenylmercury	375	6,810
Dimethylmercury	33	4,620

2.1 INORGANIC MERCURY

The inorganic mercury category is mentioned first because most of the mercury in the earth's crust occurs in the form of mercuric sulfide (cinnabar=HgS). Mercury has been mined in Europe for about 2,500 years. Carthaginian settlements in Spain had begun mining cinnabar in Spain by at least 300 BC (Dudley 1960). The mines at Almaden (Spain) and Idria (Slovenia) have been in use essentially continuously for more than two millennia.

Greek historians describe mercury poisoning among miners, and in Rome, consignment to work in mercury mines was a death sentence. Pliny the Elder (before he got too close to the Vesuvius eruption) described mercury poisoning ca 50 AD.

In soil and sediment, inorganic mercury, particularly mercuric sulfide (HgS), plays an important role as a "sink" for mercury, and mercuric ions that reach the sediment undergo a competition between naturally occurring sulfur (which can trap mercury and reduce its bioavailability) and bacteria (which methylate the mercury and increase its bioavailability).

Inorganic forms of mercury have had many uses including as fungicides, medicinals, skin-lightening creams, and in paint and tattoo pigments (Goldwater 1972). Prior to the mid-1900's, calomel was widely used to treat digestive disorders, and it has been suggested that an acute dose of calomel hastened Napoleon's death (Mari et al. 2004). Calomel (mercurous chloride, Hg_2Cl_2) was administered to infants as a "teething powder" to reduce discomfort. In infants, it produced an epidemic of "Pink Disease" or acrodynia, a serious illness which included bright pink extremities and desquamation (peeling skin; Warkany and Hubbard 1948). This use was discontinued by about 1950.

Mercurials were also used to treat infections such as syphilis. The medicinal uses of mercury have been banned in developed countries for decades (Goldwater 1972), but cases arising from medicines imported from the Orient, continue to occur (Weinstein and Bernstein 2003).

The corrosive properties of mercuric nitrate were widely used to make break hairs into short lengths for making felt hats. The kidney is a primary target organ. This is widely assumed to be responsible for the term "Mad as a Hatter," due to the emotional lability (erethism) characteristic of inorganic mercury poisoning.

Inorganic mercurial compounds generally have low volatility, and dermal absorption is negligible (see Table 3). Nonetheless, occupational poisonings occurred regularly until improvements in industrial hygiene were made.

2.2 ELEMENTAL MERCURY

Although some free elemental mercury does occur in nature, mercury is mainly extracted and purified from cinnabar by heating and condensation. Elemental mercury is familiar as quicksilver, a liquid substance that generations of children enjoyed playing with because of the propensity to breakup into fine droplets and then coalesce. Inhalation of vapor is the pathway of concern. The main neurotoxic effects are tremor and a behavioral syndrome (erethism) characterized by pathologic shyness alternated with combativeness. This differs from the cognitive effects of organic mercury poisoning. Exposure to elemental mercury is now considered highly hazardous, and great expenditures of funds are made to contain, control, or eliminate elemental mercury, particularly after spills. Mercury-containing batteries have been banned in many countries. Mercury in household and even hospital thermometers has been reduced, and some states (such as New Jersey) have banned the sale of mercury thermometers.

Mercury switches used in automobiles, appliances, and even children's shoes, are being phased out or reduced. Elemental mercury is also used in a variety of cultural and superstition rituals called attention to by Wendroff (1990), particularly in Afro-Caribbean cultures, although mercury was also valued for good luck by Andean Indians in Peru.

2.3 ORGANIC MERCURY

Although there are many actual or potential organic compounds that contain mercury, only four types will be mentioned here: phenylmercuric acetate, and the following alkylmercury compounds: ethylmercury (including thiomersal also spelled thimerosal), methylmercury (actually monomethylmercury [MeHg]), and dimethylmercury (DMHg). The commonest form of organic mercury in the environment is monomethylmercury (MeHg), and the extensive literature on MeHg generally ignores the presence of small amounts of DMHg. The nervous system and kidney are the main targets, and some organomercurials were commonly used as diuretics (through their role as kidney poisons) into the 1970's.

2.4 PHENYLMERCURIC ACETATE

Phenylmercuric acetate (PMA) was widely used as a paint additive, both as an anti-fouling agent in marine paints applied to boats and to prolong shelf-life of latex paint. It was also used as a fungicide and seed dressing, although to a lesser extent than ethyl- and methyl- mercury compounds. It has lower human toxicity than MeHg. The use in indoor paint was banned in 1991. Hirschman et al. (1963) identified mercury in paint as a source of childhood exposure producing acrodynia, although the main cause of this disease was mercurous chloride applied directly to children. PMA breaks down in the body to inorganic mercury and is, therefore, less toxic than the alkylmercury compounds (Goldwater 1972, ATSDR 1999).

2.5 ETHYLMERCURY

Ethylmercury compounds have lower toxicity than methylmercury, but still retain the biocidal properties that account for the widespread use as preservatives. A variety of ethylmercury compounds have been used commercially as fungicides and preservatives. The most widely used of these is thiomersal (the approved World Health Organization's name for this sulfur-containing compound). However, it is more commonly spelled, or misspelled, as "thimerosal" in the United States. This comprises a benzoic acid moiety linked to ethylmercury through a sulfur atom. Thiomersal is still widely available as an antiseptic (merthiolate) and as a preservative in vaccines. Because of concern over the dose of organic mercury received by infants, thiomersal has been phased out of childhood vaccines in developed nations, beginning around 1999.

Ethylmercury compounds, particularly ethylmercury-p-toluene sulfonanalide were used as fungicides for seed dressings, and contributed to epidemics of poisoning in Iraq. Ethylmercury is only slightly less toxic than MeHg. It is significant that two secretaries working about 5 m from

a container leaking diethylmercury in a pesticide warehouse were fatally poisoned (Hill 1943, cited by Nierenberg et al. 1998).

2.6 MONOMETHYLMERCURY (MEHg)

This is the form of organomercurial most widely found in nature. There are many toxicologic experimental studies of MeHg, usually using methylmercury chloride, and there are many studies of MeHg in the environment. A variety of MeHg compounds was used as seed dressings to prevent grain from turning moldy, and methylmercury dicyandiamide was implicated in some of the epidemic poisonings (see below). There are minute quantities of MeHg in the atmosphere and in water, but most MeHg in the environment occurs in living organisms. Except for occupational exposures, virtually all human exposure to MeHg occurs from eating fish (ATSDR 1999).

Elemental and inorganic mercury that reaches water bodies settles to the sediment where it is converted by anaerobic bacteria to methylmercury. Methylmercury has high bioavailability and undergoes bioamplification up the food chain, until top level predatory fish accumulate relatively high concentrations in their tissues (see Minamata Disease below). The bioconcentration factor from mercury in water to mercury in top level predatory fish often exceeds 10,000. This process of biomethylation and bioamplification has been known since the late 1960's (Jensen and Jernelöv 1969) and is not covered in detail here, although they postulated that the first step in methylation was to form DMHg which was converted to MeHg in the presence of excess mercury.

By 1970, the importance of MeHg in fish was well-established (Expert Group 1971).

2.7 DIMETHYLMERCURY (DMHg)

Dimethylmercury (H_3C-Hg-CH_3) is the most dangerous mercury compound, and it is one of the most toxic compounds known. It is also one of the least known. It is a dense flammable liquid at ambient temperature. It is highly volatile and has a slightly sweet smell. It is insoluble in water, but is quite soluble in ether or alcohol. The only commercial role for DMHg is its use in laboratory studies and instrument calibration.

Information on the efficiency of absorption through the skin, lungs, and intestinal tract is very limited. Dermal absorption is higher for DMHg than for MeHg, and it is likely that inhalational and intestinal absorption would be at least as high as for MeHg. Once absorbed, DMHg is either rapidly exhaled or converted to MeHg by demethylation (Östlund 1969).

Permeation tests were performed by a laboratory, indicating that dimethylmercury penetrates latex gloves within 15 sec (Blayney 2001).

There have been several reports of workers exposed to DMHg, and three fatal poisoning events attributed to dimethylmercury (DMHg) have been published (Table 4). Overall, however, there

is relatively little information on DMHg, most focusing on a single case (see discussion of the Wetterhahn poisoning below). The paucity of study of DMHg can be inferred from the fact that there are different values published (see Table 2) for characteristics as simple as density (2.96 g/cm^3 and 3.19 g/mL) and boiling point (92 – 96 °C).

Table 2. Some Properties of Dimethylmercury

Characteristic	Value	
Density	2.96 g/cm^3; 3.19 g/mL	
Conversion	1 ppm = 9.43 mg/m^3	1 mg/m^3 = 0.106 ppm.
Molecular weight	230.66	
Specific Gravity	3.069	
Vapor pressure	58.8 mm at 23.7 °C	
Boiling Point	Variously given as 92, 93, 96 °C	

Sources: *J. Inorg. Nucl. Chem* 1961; 20,340; Merck (1989); ATSDR (1999):369; Toribara et al. (1997)

A comprehensive survey of environmental data on the occurrence of DMHg was NOT performed for this report. There are numerous studies of organic mercury in the abiotic (water, soil) and biotic (invertebrates, fish, birds, mammals) environment, but most analyses report only total mercury or total and methylmercury. Yet when analyzed for, DMHg is sometimes present (Wasserman et al. 2002). DMHg accounts for less than 3% of the total dissolved gaseous mercury in water (Vandal et al. 1991). Most of the mercury in fish tissue is MeHg; there is a slight or negligible amount of DMHg (ATSDR 1999:422).

ATSDR (1999) reports that mercury has been reported at 714 of 1,467 (49%) sites on the National Priorities List, but DMHg has been identified at only two sites. However, analytic protocols would not favor discovery of DMHg.

2.7.1 Cases of Dimethylmercury Poisoning

Siegler et al. (1999) wrote: "To our knowledge, dimethylmercury has been reported in only three cases of human poisoning, each proving fatal [see Table 4]. Very small amounts of this highly toxic chemical can result in devastating neurological damage and death." Dimethylmercury was synthesized in the mid-1800's (as cited by Nierenberg et al. 1998 from report in *Q.J.Med.* NS9,193, 1940). Two workers died from a spill of this material (ca 1865), and these cases were published by G. N. Edwards in 1866. In the early 1970's, a Czech chemist who synthesized about 6 kg of dimethylmercury suffered a fatal cumulative exposure over a period of three months (*Int. Arch Arbeitsmed* 33, 323, 1974; cited by Nierenberg et al. 1998). In 1997, Karen Wetterhahn, PhD, a Dartmouth College chemist, died from DMHg poisoning, and this case will be described in detail below.

3.0 ORGANIC MERCURY EXPOSURE AND POISONING

3.1 MERCURY EXPOSURE

Historically, most mercury exposure has occurred from inorganic or elemental mercury exposure in mining, industry, or agriculture (including both occupational exposure, and exposure from wastes or products). As these have come under control, most attention has shifted to methylmercury in the environment. In developed nations, coal-fired power plants are now a primary source of atmospheric mercury that eventually falls out (wet deposition) and reaches water bodies where it is converted to methylmercury and is bio-amplified through the food chain, reaching high concentrations in large fish (National Research Council 2000). Fish consumption is the only important source of methylmercury exposure for most of the population (Clarkson 2002). Attention has focused on the development of the fetal nervous system as the most sensitive target, and regulations and fish consumption advisories have been designed with this endpoint in mind, although the values and standards vary somewhat from agency to agency and country to country (National Research Council 2000, Agency for Toxic Substances and Disease Registry [ATSDR] 1999).

For the purpose of this report, only adult exposure is being considered.

3.2 ABSORPTION

The different classes of mercury compounds have different pathways of exposure and absorption as shown in Table 3. The information on DMHg is particularly limited.

Table 3. Efficiency of Absorption of Different Forms of Mercury, Indicated as Percent of Mercury Passing from Environment into the Blood Stream.

Form of Mercury	Inhalation	Ingestion	Dermal
Elemental Hg (Hg^0)	Volatile at ambient temperature. Very high absorption >80%	Negligible < 0.1% of ingested Hg is absorbed in intestinal tract.	Very low (Clarkson 1997)
Inorganic Hg (Hg^+, Hg^{++})	Low volatility. But fine dusts may be inhaled. More common in industrial settings.	10%	Slight (Goldman et al. 2001)
Monomethylmercury MeHg	Estimated at 80%	At least 95% (Aberg et al. 1969)	Moderately high, but not as high as DMHg.
Dimethylmercury DMHg	No information found, but no reason to assume it would be lower than for MeHg	No specific information but presumably at least 95%	Very high, approaching 100%

3.3 CHRONOLOGY OF MERCURY POISONING

Table 4 provides a chronology for several different kinds of mercury poisoning, beginning with the description by Pliny the Elder (ca 50 AD) of mercury poisoning among miners. The history of organic mercury poisoning dates back to the mid-1800's, and a death from DMHg has been documented from 1865. After World War I, organomercurial compounds were introduced as fungicides, and cases of mercury poisoning were reported. In 1942, two secretaries working at a grain warehouse died from exposure to an ethylmercury fungicide. But the history of modern organic mercury poisoning dates from the 1950's, when many fishing folk in the Minamata Bay area of Kyushu, southern Japan, experienced devastating neurologic illness from unknown cause. Infants born to affected mothers suffer severe physical damage and mental retardation (see more details below). The source was contaminated fish.

In the 1960's, Swedish biologists documented many bird deaths due to consuming mercury-treated grain, and in the late 1960's countries such as Sweden began banning the use of mercury fungicides on grain. Nonetheless, major epidemics of grain-related mercury poisoning did occur.

In the 1990's, attention focused on several aspects of mercury "poisoning" including its possible role in autism (from thiomersal in vaccines) and neurodegenerative diseases such as Parkinsonism and Multiple Sclerosis (from dental amalgams). There is no consensus on these putative relationships. The removal of thiomersal from childhood vaccines, beginning around 1999, affords the opportunity to study whether there will be a decline in autism cases diagnosed in the coming years.

Table 4. Chronology of Different Types of Mercury Poisoning (2 Sheets)

Year	Elemental/inorganic	Minamata and fish Methylmercury	Grain-related Organic Mercury	Dimethylmercury
50 AD	Pliny Elder describes Hg poisoning in miners			
1700	Ramazzini describes elemental and inorganic mercury poisoning			
mid-1800's	$HgNO_3$ used in felt hat industry.			In 1865 two laboratory workers died weeks after synthesizing DMHg. (Nierenberg et al. 1998).
1940's			In 1942, two secretaries in Calgary, Canada, die from diethylmercury (apparently inhalation) stored for grain treatment (Hill 1943). A few cases reported in Sweden from eating dressed seed.	
1950's		Many fisher folk experience strange illness. Congenital		

Table 4. Chronology of Different Types of Mercury Poisoning (2 Sheets)

Year	Elemental/inorganic	Minamata and fish Methylmercury	Grain-related Organic Mercury	Dimethylmercury
		Minamata disease occurs.		
1955		Some people stopped eating fish		
1956			First known Iraq epidemic (EtHg)	
1960		Kurland et al. (1960) publish paper documenting MeHg as cause of Minamata Disease, traced to Chisso Chemical Plant	1,000 cases, 220 to 370 hospitalized (depends on source) Ethylmercury-p-toluene sulfonalide	
1963-1965			Guatemala episodes from MeHg dicyandiamide	
1965		Epidemic of MeHg poisoning from fish at Niigata, Japan		
Late 1960's		Recognition that inorganic mercury is biomethylated to MeHg in sediments (Jensen and Jernelov 1969)	Huckleby family poisoned by eating hogs fed MeHg treated grain. Studies of avian poisoning from grain.	
1971-1972			Iraq epidemic (Bakir et al. 1973) 6,000+ hospitalized 459 deaths among hospitalized. Many countries ban use of mercury-fungicide on grain.	Lab worker dies after synthesizing 6 kg of DMHg.(Pazderova et al. 1974)
1990's	Most mercury batteries banned in most developed countries.	Clinical case reports of low level and generally reversible effects in fish consumers (Hightower and Moore 2003; Gochfeld 2003)		
1996-1997	Substantial controversy over safety of mercury amalgams.			Karen Wetterhahn poisoned by DMHg in laboratory (Aug 1996), died June 1997
2000		NRC (2000) reviews conflicting data on neurodevelopmental effects of MeHg.		

3.4 SPECTRUM OF METHYLMERCURY POISONING

This section covers the general features seen in methylmercury poisoning events. It is believed that dimethylmercury is first demethylated to methylmercury, which enters the brain (Östlund 1969), and is then converted to inorganic mercury, so that the features described here apply to DMHg as well as MeHg. Table 5 summarizes the sequence of symptoms and their reversibility, based mainly on the Iraq (1971-1972) epidemic.

Methylmercury poisoning is characterized by a long latency period. This is particularly prominent with the DMHg cases, where five months elapsed between exposure and symptoms (see Wetterhahn case below). For monomethylmercury exposure, the latency is "weeks or months" (Bakir et al. 1973), and this was evident in the Iraq epidemic (see below) where the exposure period was well-established.

There is a fairly consistent spectrum or sequence of health effects that is apparent when the single DMHg (1996-1997) laboratory fatality is compared with the larger published series of cases from a MeHg poisoning episode in Iraq (1971-1972). However, the laboratory fatality had a blood mercury level of 2,000 µg/L when first discovered so provides little information on low-level effects.

The earliest symptom is usually paresthesia, the sensation of tingling in the lips and then pins-and-needles in the hands and feet. Clinical examination at this stage can sometimes detect reduced sensitivity to light touch in fingers, toes, and lips. In the Iraq epidemic, paresthesias occurred in people with levels below 100 µg/L in blood mercury level (Bakir et al. 1973), but the lowest level at which paresthesias occurred was not documented.

The second symptom is some form of motor-incoordination. In fish-eaters, clumsiness in the hands and fingers is an early finding (Gochfeld 2003), but in the Iraq epidemic this was not reported. Rather, ataxia or clumsy stumbling gait was noted, in some people with blood mercury levels below 100 µg/L, and in 100% of those who exceeded 3,000 µg/L.

Higher level poisoning is manifest as slurred speech (dysarthria), reduced peripheral vision (constricted visual fields or "tunnel vision"), blindness, deafness, coma, and death. As far as can be told from the literature, once cases have progressed to visual damage, complete recovery is unlikely to occur. The earliest stages, however, appear to be all or partially reversible. Visual symptoms include narrowed visual fields or flashing lights. In Iraq, this occurred at blood mercury levels above 500 µg/L.

Dysarthria or difficulty forming clear speech occurred in Iraqi subjects who exceeded a blood mercury level of 1,000µg/L, and deafness ensued in a few people above 2,000 µg/L. The threshold for death was 3,000 µg/L.

Table 5. Sequence of Symptoms and Probability of Reversibility for Methylmercury and Dimethylmercury Poisoning

Symptoms and Sequence	Likelihood of reversibility
Tingling in lips, fingers, toes	High
Clumsiness of fine motor movements	Fairly high
Clumsiness of gait, staggering	Probably not complete
Constricted visual fields	Not complete, probably not fatal
Difficulty speaking	Not complete, probably not fatal
Blindness, Deafness	No recovery, but not necessarily fatal
Awake but unable to move	Viable for decades in congenital cases, but no reversibility
Comatose	Usually progresses to death, but may last for months or years.

The most dramatic pathologic changes are seen in the cerebellum with severe focal necrosis, which was first described in 1954 (Hunter and Russell 1954). Hunter-Russell Syndrome is a synonym for Minamata disease. What is lacking from the Iraq data is information on the low-level exposures and effects that would have occurred at blood mercury levels of 20 µg/L (usually considered the upper limit of "normal"), or 50 µg/L at which other researchers have reported subtle neurobehavioral effects.

3.5 MINAMATA EPIDEMIC (MEHg FROM FISH)

In the mid-1950's, a mysterious disease occurred among the fishing families of Minamata Bay. A variety of neurologic symptoms occurred, and babies were born with the findings of severe cerebral palsy and severe mental retardation. The diseases occurred also in cats that danced and screamed and died. Even fish developed behavioral abnormalities. By 1955, many fishing families had stopped eating their catch from the Bay. By 1956, it was apparent that this was a serious human epidemic, and investigation was undertaken. Data on congenital cases of Minamata Disease were obtained from 1955-1959. Fishing was banned in Minamata Bay in 1957. It was, however, several years before methylmercury was identified as the cause of the disease, and the Chisso Company, which still operates a large chemical company at Minamata, was identified as the source. Waste mercury, including methylmercury itself, from use of mercury catalysts in chemical production, had been discharged into Minamata Bay.

The number of cases of Minamata Disease became a topic of major controversy. The early official tallies placed the number of cases at 121 with 46 deaths. This included 23 congenital cases with two deaths. Political and financial considerations have influenced who qualifies for labeling as "Minamata Disease" with entitlement to compensation. The decision to expand the definition included over 1,100 people as Minamata cases (Takizawa 1979). Plaintiffs have placed the toll much higher with estimates of 2,000+ or even 20,000 having some degree of MeHg poisoning. Among the congenital cases or children affected early in life, some survived for two decades although they had negligible ability to interact or care for themselves. The story of Minamata is graphically portrayed by Smith and Smith (1975).

Table 6. Epidemics or Cases of Organic Mercury Poisoning

Location	Year(s)	Context	Exposure	Outcome
England	1865	Synthesis of DMHg	Probably direct contact with DMHg	2 laboratory assistants died
Calgary, Canada	1942	Warehouse storing ethylmercury pesticides	Probably direct contact or inhalation with ethylmercury	2 secretaries died
Minamata, Japan	1950's	Fishing families eating fish	Chemical effluent contained MeHg	Official report 121 cases (includes 23 prenatal) and 46 deaths. Much higher numbers reported (>1,100) (Takizawa 1979).
Iraq	1956	Use of dressed seed for bread	Ethylmercury-p-toluene sulfanilate	100 cases 14 deaths in hospitals
Iraq	1960	Use of dressed seed for bread	Probably ethylmercury	221 hospitalized
Pakistan	1961	Dressed seed	Mixture of phenylmercuric acetate and ethylmercury chloride	100 cases
Guatemala	1963-1965	Use of dressed seed for bread	MeHg dicyandiamide	45 cases, 20 fatal in 1965 (sporadic cases earlier)
Niigata, Japan	1965	Fishermen around Agano River	MeHg from industrial release	47 cases, 6 deaths
Iraq	1971	Use of dressed seed for bread	Treated seed with MeHg	6,000+ hospitalized and 469+ fatalities based only on those hospitalized
Czechoslovakia	1971	28 year-old chemist synthesizing DMHg	Mixed exposure to DMHg	1 chemist died
Albuquerque, NM	1969	Huckleby family ate hogs fed grain sweepings	MeHg dicyandiamide treated grain	1 congenital "Minamata" disease and 3 children irreversibly poisoned.

3.6 ORGANOMERCURIAL POISONING FROM GRAIN

Several organomercurials have been used as anti-fungal agents on seed grain stored over the winter. The first known cases of poisoning from consuming fungicide-dressed seed occurred in Sweden in the 1940's (Engleson and Herner 1952). Ethylmercury and phenylmercuric acetate-treated grain caused an outbreak of mercury poisoning (about 100 cases) in Pakistan in 1961, of which 34 were hospitalized and at least four died. Farmers made bread out of seed intended for planting. That syndrome was characterized by malaise and lethargy, followed by burning of the mouth, nausea and vomiting, and thirst. These patients experienced difficulty walking and

cognitive impairment and slurred speech. The most serious cases were unable to stand, see, or hear and had spontaneous sucking and chewing movements which continued in coma (Haq 1963). The phenylmercury contributed symptoms reminiscent of inorganic mercury poisoning coupled with the organic mercury syndrome caused by the ethylmercury.

Epidemics attributed to an ethylmercury sulfonamide occurred in Iraq (1956, 1960; Jalili and Abbasi 1961). In these epidemics, farmers also used seed intended for planting to make bread. Methylmercury dicyandiamide (Panogen) was used to treat wheat in Guatemala. People who ate the wheat became ill, with a 100% attack rate and a 44% fatality rate. A family in New Mexico was poisoned by eating pork from hogs they had fattened on mercury-treated grain (MeHg dicyandiamide; Curley et al. 1971). The last is the only United States MeHg event; an infant was born with severe mental retardation to the asymptomatic mother, and three children suffered irreversible and severe neurotoxicity (Curley et al. 1971).

The most serious and best-studied grain-related epidemic occurred in Iraq in 1971-1972 where the published death toll reached 459. Although Iraq, spanning the "fertile crescent" has been known as the "bread-basket" of antiquity, there have been periodic crop failures and famine. Following such a crop-failure, international agencies provided large quantities of seed grain to Iraq which was distributed to farmers for spring planting. Most of the grain came from North America (United States and Mexico) and the warning labels were in English or Spanish. The mercury-treatment was also signified by the skull-and-crossbones icon, which, however, was apparently unfamiliar to Iraqi farmers (Clarkson 1997). The mercury-treated grain had been mixed with a pink dye as further warning---a standard practice in Europe and North America. The farmers washed off the red-dye and assumed that any poisonous properties were washed away as well. Much of the grain was processed directly into bread, and over a two to three month period, large quantities of methylmercury were consumed by large numbers of people.

The main period of intake was November-December 1971, and people began getting ill in January 1972. Most of the serious nervous system damage was irreversible (Clarkson 1997). The Iraq epidemic provided the first quantitative exposure and outcome data on organomercurial poisoning, particularly for intra-uterine exposure and outcome in fetuses (Amin-Zaki et al. 1974). However, since the epidemic was not discovered until after the main exposure had ended, much of the exposure data is retrospective, hence there remained large uncertainty regarding the dose-response curve (Cox et al. 1995). Bakir et al. (1973) developed dose response curves for paresthesia, ataxia, visual disturbance, dysarthria, deafness, and death.

The mean lethal body-burden of MeHg was estimated in the range of 200-312 mg of mercury, and the median lethal dose was 400-600 mg (Bakir et al. 1973). Table 7 is modified from Table 4 in the Bakir et al. (1973) paper and shows the proportion of cases with each symptom at different blood mercury levels. Table 8 shows the body burden threshold for each of the symptoms.

Table 7. Proportion of Cases with Each Symptom at Different Blood Mercury Levels

Hg in Blood (µg/L)	# of cases	Days Ingested	Latency	% paresthesia	% ataxia	% visual changes	%death
0-100	21	43	--	9	5	0	0
101-500	19	43	--	5	0	0	0
501-1,000	19	43	16	42	11	21	0
1,001-2,000	17	41	18	60	47	53	0
2,001-3,000	25	55	26	79	60	56	0
3,001-4,000	17	58	32	82	100	58	17
>4,000	7	68	38	100	100	83	28

Note: Modified from Bakir et al. (1973: Table 4) showing percent of symptoms associated with different peak blood levels inferred from hair samples. The threshold for paresthesias was about 25 mg total Hg body burden and for death about 200 mg.

Table 8. Threshold for Each Symptom in Terms of Body Burden of Mercury (total milligrams)

	Estimated body burden of total mercury in milligrams at the time of onset of symptoms.	
SYMPTOM	Low estimate	High estimate
Paresthesia	25 mg	40 mg
Ataxia	50 mg	78 mg
Dysarthria	70 mg	110 mg
Deafness	150 mg	240 mg
Death	160 mg	250 mg

Note: Derived from Figure 5 in Bakir et al. (1973)

3.7 KAREN WETTERHAHN CHRONOLOGY (DMHg IN LABORATORY)

Karen Wetterhahn, PhD, a professor of chemistry at Dartmouth College in Hanover, New Hampshire, was a world famous metal chemist and probably the world expert on the intracellular redox cycling of chromium. Having collaborated with her on a chromium conference, the author knew her to be a knowledgeable and thoughtful scientist, with a dedication to hands-on laboratory work. When she became ill in January 1997, she was diagnosed with mercury poisoning, and then she tried to reconstruct the events that led to her poisoning (see below).

The following has been assembled from personal communications, newspaper accounts, and papers published by Blayney et al. (1997), Nierenberg et al. (1998), Siegler et al. (1999), and Toribara (2001).

According to her laboratory notes and personal recollection, her only exposure to DMHg occurred on August 14, 1996. She became ill in mid-January 1997 (154 days later), lapsed into a coma within three weeks, and died five months later (June 1997) despite extremely aggressive treatment.

According to a newspaper account (see Appendix A), Wetterhahn was studying the way mercury ions interacted with DNA repair proteins, and was using [$Hg(CH_3)_2$] as a standard reference material for 199Hg Nuclear magnetic resonance measurements.

On August 14, 1996, Wetterhahn was using dimethylmercury to calibrate the Nuclear Magnetic Resonance (NMR) instrument. She spilled "a drop" (Toribara 2001) or "several drops" (Nierenberg et al. 1998) on her latex gloved hand. The various reports mention one to five drops, which yields an estimated 0.1 to 0.3 mL. She cleaned up the spill and removed and disposed of her glove, but not before the DMHg penetrated the glove and her skin. There was a five-month lag before symptoms became apparent. Table 9 provides a chronology of biomarkers reported by Nierenberg et al. (1998) and Toribara (2001).

In mid January 1997, "Wetterhahn first noticed some difficulties with her balance...then experienced numbness in her fingers and diminished hearing and sight," according to *The Dartmouth* cited by the *Rutgers Daily Targum* (February 26, 1997). Note that this is slightly different from the classical sequence in which paresthesias precede ataxia. Dr. Wetterhahn recognized her neurologic deterioration, with upper-extremity dysmetria, dystaxic handwriting, scanning speak, and awkward gait. The dysmetria (difficulty putting finger on an object) and handwriting abnormality are consistent with my observations in a patient who got mercury poisoning from consuming fish (Gochfeld 2003).

Dr. Wetterhahn went to the emergency room January 20, 1997, and was admitted. It was after admission that she reported tingling of her fingers, flashes in both eyes, tinnitus, and increasing speech difficulty. The diagnosis of mercury poisoning was established in the ensuing week. Chelation therapy was begun on January 29, 1997, resulting in rapid mobilization of mercury, very high blood levels, and high urinary output (Table 9). Over the next weeks, her visual fields contracted. She lost vision and hearing, and neuroaudiologic testing revealed that latter loss occurred at the brain level rather than in the ear or acoustic nerve (i.e., it was central rather than peripheral; Musiek and Hanlon 1999); they concluded "Dimethylmercury poisoning, in this case, resulted in compromise of the auditory neural system with little effect on the sensory (cochlea) mechanism."

She quickly (over a period of three weeks from January 15 to February 8) had cognitive impairment, and lapsed into coma, despite (or perhaps because of) the very vigorous treatment which resulted in temporarily very high circulating mercury levels. She died on June 8, 1997.

At the time of diagnosis in late January, Wetterhahn's blood mercury level was 80 times the toxic threshold. Her hair mercury level was in the highest range recorded at Minamata, almost 1,100 ppm. At the time of death, her brain showed extreme shrinkage and necrosis, and the concentration of mercury in some parts exceeded 3,100 ppb.

3.7.1 The Calculation of Dr. Wetterhahn's Exposure

Dimethylmercury has a molecular weight of 230, and mercury has a molecular weight of 200, thus 87% of the compound is mercury, and the organic component ensures essentially complete and rapid absorption through the skin.

Typically, there are 20 drops of liquid to one mL; hence, if she remembered the spill as one to two drops, it is conservative to estimate that her exposure was 0.1 mL (about two drops).

The specific gravity of dimethylmercury = 3; hence, 0.1 mL of DMM weighs 0.3 g, of which 0.26 g would be mercury. Absorption of 0.26 g (260,000 micrograms) was sufficient to elevate blood levels and eventually brain levels above a lethal limit. The total body dose, assuming a 60-kg body weight, would have been 0.43 mg/kg. This would have occurred as a very short-term, peak exposure.

Nierenberg et al. (1998) also tried to estimate her initial dose, noting that her estimated body burden was about 336 milligrams at the time of her diagnosis. This amount would be contained in 0.11 mL of DMHg liquid. However, using the measured half-life of mercury in Dr. Wetterhahn's hair of 75 days, and the 154 days between exposure (August 15th) and diagnosis (January 29th), they estimated that the original exposure was probably four times higher (two half-lived=4 fold), or about 0.44 mL. This would correspond to about 10 drops rather than one to five drops.

What makes dimethylmercury so toxic is its effectiveness as a vehicle for delivering mercury, first by penetrating latex, secondly by penetrating the skin and entering the circulation, and thirdly by penetrating the blood brain barrier (although it may penetrate mainly after conversion to MeHg).

3.7.2 Hair Analysis for Dr. Wetterhahn

Single strand hair analysis can be performed by X-ray fluorescence (XRF). This allows measurement of mercury at each point along the hair. Hair typically grows at a rate of about 1.1 cm per month. Toribara (2001) analyzed Dr. Wetterhahn's hair in 2-mm intervals, each point corresponding to a few days growth. The hair collected on January 29, 1997 shows a very low level near the tip (corresponding to the pre-exposure period), and a sudden sharp peak rising at an astounding rate of about 50 parts per million per day, until a peak of about 1,100 ppm was reached. Using the average growth of 1.1 cm per month, physicians were able to tell Dr. Wetterhahn of a huge exposure occurring about five months previously. She then recalled that she had been working with dimethylmercury briefly during the summer, which led to examination of her laboratory notebook. The notebook revealed an entry on August 14, 1996, the only day on which she had used DMHg, and her notation that she had spilled a drop on her rubber glove while weighing out an aliquot of DMHg for calibration. Documentation of this date

Table 9. Chronology of Biomarkers for Karen Wetterhahn

	Whole Blood	Urine	Hair	Events
"Normal values"	**Normally less than 8 µg/L.**	**<5 µg/L or <5 µg/day**	**<0.26 ppm. 90% o f population is below 1 ppm**	
"Toxic level" cited by Nierenberg et al.1998)	> 200 µg/L	>50 µg/L	50 ppm (although other evidence suggests <15 ppm, Gochfeld 2003)	
August 14, 1996			1,100 ppm reached by about August 20	Date of exposure
January 15, 1997			About 350 ppm (inferred from graph in Toribara 2001)	Approximate onset of symptoms
January 20, 1997				Admitted to Hospital
January 29, 1997	1,000 µg/L	Pre-chelation 257 µg/24h		Diagnosis made and chelation started
January 31, 1997	4,000 µg/L	Post-chelation 39,800 µg/24 hrs		
Early February	2,230µg/L to 2,070 µg/L (after rebound)		2,000 ppm post-chelation	Exchange transfusion performed
February 6, 1997				Became unresponsive
April 3, 1997			About 500 ppm.	2nd hair sample
June 8, 1997				Died

allowed "calibration" of the hair sample. This yielded a growth rate of 0.44 mm per day (or about 1.3 cm per month), slightly faster than average.

Chelation treatment was started on January 29, 1997, in an attempt to pull the mercury out of her tissues. A second hair sample was taken on April 3, 1997, and shows a second and higher peak beginning at the end of January, and rising to almost 2,000 ppm in the first days of February, before gradually declining to 500 ppm in early April. This documents the massive release of mercury into the circulation (which peaked at 4,000 µg/L) from the chelation treatment (Toribara 2001), which the author believes accelerated her decline.

3.7.3 Connecting the Wetterhahn Case to Toxicology

There are remarkably few studies of dimethylmercury itself, compared to innumerable studies of methylmercury. Mori et al. (2000) dosed rats with 5 mg/kg/day (DMHg) for 12 consecutive days, and documented neuronal degeneration and calcium deposition, particularly in the cerebellum. The total dose in these rats would have been about 100 times higher (on a body

weight basis) than Dr. Wetterhahn received. Östlund (1969) dosed mice with MeHg and DMHg and traced their distribution and elimination. DMHg was either exhaled or demethylated to MeHg.

3.8 LATENCY

The common denominator of all of these DMHg cases, as well as cases of MeHg poisoning (Weiss et al. 2002), is the long latency between exposure and clinically detectable effect. Exposure may be a single occurrence (as in the Wetterhahn case below) or a cumulative exposure, eventually exceeding some toxic threshold, as in the Minamata poisoning event from MeHg in fish. In the Iraq epidemic (from grain), symptoms did not appear until several weeks at the earliest, and new symptoms appeared months after the exposure ceased. An experimental study of monkeys dosed to MeHg resulted in new symptoms appearing years after the exposure (Weiss et al. 2002).

The long latency has very significant impact on worker exposure and industrial hygiene. By the time symptoms are manifest and are identified as organic mercury poisoning, it is likely to be too late to avert permanent damage or death.

3.9 INDUSTRIAL HYGIENE AND MEDICAL MONITORING

This report does NOT examine personal protective equipment, environmental monitoring, or medical monitoring requirements for circumstances where exposure to DMHg may occur. Information provided in Material Safety Data Sheets (Appendix C) and by vendors (Appendix D) does NOT provide appropriate guidance on the equipment needed for handling DMHg or for working in environments where DMHg may be present. The recommendation from Occupational Safety and Health Administration (OSHA) (Appendix B) and Blayney (2001) is to use high-resistance laminate gloves such as SilverShield or 4H which should be protected under a pair of long-cuffed neoprene, nitrile, or similar heavy duty glove. The requirement to work under a hood is also inadequate in the light of the high volatility and toxicity of DMHg. Neither of these may be practical in an outdoor maintenance or remediation scenario. Further examination of these issues is essential.

3.10 RELEVANT ANALYTIC ADVANCES

This report also does NOT include a review or discussion of new analytic approaches for detecting, speciating, identifying, and quantifying mercury compounds. It is apparent, however, that analytic methodology for ultra-low detection levels and for speciation in a variety of environmental and biologic matrices is being pursued and can be helpful in environmental and medical monitoring. These new techniques include the development of new derivitization procedures (Monperrus et al. 2004), solid-phase extraction-gas chromatography-mass spectrometry (Munoz et al. 2004), biosensors (Martinez-Neira et al. 2005), enhanced atomic fluorescence spectrometry (Tseng et al. 2004), and ICP-time-of-flight mass spectrometry (Jitaru and Adams 2004). Simultaneous identification of mercury with other cations also attracts

attention (Gomez-Ariza et al. 2004, Monperrus et al. 2004). An *in vitro*, bioengineered bacterial system developed as a sensor, distinguished MeHg, phenylmercury, and DMHg, although the sensitivity was lowest for DMHg (Ivask et al. 2001). These are mentioned mainly to show that there are very active developments in new techniques of mercury analysis.

3.11 INDUSTRIAL HYGIENE SAMPLING

There are very few laboratories that have developed reliable sampling and analytical methods for DMHg in either vapors or liquid samples to characterize the workplace to support appropriate Industrial Hygiene determinations. One firm, (Frontier Geosciences, Inc., Seattle, Washington) has developed a proprietary method that uses specially prepared sorbent traps to collect mercury and DMHg, and extracts those compounds into a liquid and completes the analysis of the liquid extract to determine the levels present. Similarly, they can analyze liquid samples directly for mercury and DMHg. Frontier Geosciences has provided these analytical services to many environmental cleanup projects, and were the principal analytical resource used by the Savannah River Site to characterize the presence and the extent of mercury and DMHg present in their radioactive waste storage tanks and supporting waste processing systems.

4.0 OCCUPATIONAL EXPOSURE LEVELS

NIOSH, AGCIH, and OSHA have all recognized the extremely hazardous nature of the alkyl mercury compounds and have established very low worker exposure guidelines for these materials. As discussed earlier, the primary hazard is absorption of liquid DMHg through the skin. Once absorbed, it appears that the DMHg is quickly and completely converted to MeHg which is then absorbed by the central nervous system. The primary difference between DMHg and the other alkyl mercury compounds is the apparent quick and complete absorbtion of DMHg through the skin, and the high percentage of mercury that is inherent in the DMHg molecule.

Table 10 provides the currently established occupational exposure limits for alkyl mercury compounds.

Table 10. Occupational Exposure Levels for Alkyl Mercury Compounds

Agency	8 or 9 hour TWA Concentration limit	Short term (ST) (15 minute) Limit	Ceiling concentration	Other Notations
NIOSH	REL 0.01 mg/m^3	0.03 mg/m^3		Skin Notation
OSHA	PEL 0.01 mg/m^3		0.04 mg/m^3	Skin Notation
AGCIH	TLV 0.01 mg/m^3	0.03 mg/m^3		Skin Notation

Due to the apparent speed of skin penetration of the pure DMHg liquid, specific evaluation of skin protection should be conducted whenever significant amounts of DMHg is detected in the workplace breathing zones. Engineering evaluation of any condensed liquids (water or organic) present in the workplace should be conducted to determine if significant alkyl mercury compounds have been dissolved in these liquids and skin protection is warranted.

The NIOSH occupational exposure data sheet for alkyl mercury compounds is attached as appendix E.

5.0 CONCLUSIONS

All mercury compounds are toxic, hence their widespread use as biocides. Organomercury compounds have higher toxicity than inorganic mercurials or elemental mercury, mainly because of their ease of absorption and their distribution to the brain. Dimethylmercury (DMHg) is highly volatile and also readily penetrates the skin and presumably has highly efficient absorption from the lungs and GI tract. It is converted to MeHg which passes through the blood brain barrier, and produces widespread brain damage, particularly in the cerebellum. Symptoms do not become apparent until months after exposure has occurred, and all documented cases of DMHg poisoning have been fatal, hence the kinds of dose-response information available for MeHg cases does not exist.

Assuming that the one to five drop exposure experienced by Dr. Wetterhahn is a true reflection of her dose, it will be difficult to develop a threshold for this chemical. However, it is also possible that she had some unique sensitivity either genetic or from her prior work with chemicals.

Nierenberg et al. (1998) concluded: "Since dimethylmercury is a 'supertoxic' chemical that can quickly permeate common latex gloves and form a toxic vapor after a spill, its synthesis, transportation, and use by scientists should be kept to a minimum, and it should be handled only with extreme caution and with use of rigorous protective measures."

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APPENDIX A.

NEWS STORIES REGARDING THE KAREN WETTERHAHN INCIDENT

Dartmouth researcher poisoned by material she was studying

Associated Press, March 28, 1997

HANOVER, N.H. - A respected Dartmouth College professor is in the hospital after an apparent research accident left her poisoned by the toxic mercury she was studying.

Professor Karen Wetterhahn was diagnosed with mercury poisoning eight weeks ago. The college and hospital won't discuss her condition, but her family issued a statement saying treatment is continuing.

Officials from Dartmouth's Chemistry and Environmental Health and Safety departments believe Wetterhahn was poisoned sometime in August while working alone with dimethylmercury. The mercury compound has no practical uses, but Wetterhahn was using it in her studies of mercury toxicity. There also is a delay between exposure and when a victim begins feeling the effects.

No one knows for sure how Wetterhahn was poisoned, but they suspect some of the mercury touched her skin and was absorbed into her body.

John Winn, chairman of Dartmouth's chemistry department, said it was hard to tell how much she had absorbed. He was not sure whether the mercury compound soaked through protective gear or touched her skin directly.

Wetterhahn was diagnosed after tests in January showed she had an elevated level of mercury. She was tested due to numbness in her fingers, unsteady walking, difficulty in speaking, and vision and hearing problems.

Rare Form of Mercury Kills Dartmouth Chemistry Teacher
The News York Times June 11, 1997

HANOVER, N.H., June 10 - A Dartmouth College chemistry professor has died from exposure to a rare form of mercury, first synthesized more than 130 years ago.

Karen E. Wetterhahn, 48, who also had served as an associate dean and a dean at the college, died on Sunday, about 10 months after accidentally spilling a few drops of dimethylmercury on her disposable latex gloves while performing a laboratory experiment. The substance, which has no practical application, is used in research on heavy metals.

Prof. John S. Winn, chairmen of the college's chemistry department, said Professor Wetterhahn was a leader in the study of how heavy metals can initiate cancer at the molecular level. Dimethylmercury is so rare that it is only in use in perhaps 100 laboratories worldwide at any given time, he said.

Through a search of medical literature, the college determined that exposure to the substance killed two laboratory assistants in 1865, shortly after it was first synthesized, and a 28-year-old chemist in 1971.

"Karen Wetterhahn's death is a tragedy for her family and for the Dartmouth community," said Dartmouth's president, James O. Freedman

After years of study of chromium metal toxicity, Professor Wetterhahn had turned to the study of mercury in a sabbatical at Harvard University in September 1995, Professor Winn said. In the experiment at Dartmouth last August, she had used dimethylmercury to set up a standard against which to measure other mercury involved in her research.

The drops apparently spilled onto her gloves, passed quickly through the latex and were absorbed through her skin. After her illness was diagnosed in late January, the college had the latex gloves independently tested, and it was determined that the mercury could pass through in 15 seconds or much less.

Other types of gloves offer more protection, but she probably used latex to increase dexterity during the delicate procedure, he said.

In a letter to Chemical and Engineering News about the accident, Professor Winn and the other college officials recommended that heavier gloves be used during experiments, and that "medical surveillance measuring mercury concentrations in whole blood or urine" should be considered during extended use of these compounds.

Professor Wetterhahn's symptoms, which initially included difficulty with balance, speech, vision and hearing, progressed rapidly and she was in a coma from late February until her death. Although treatments were administered to eliminate the mercury in her system, they began too late to prevent irreversible damage to the nervous system, Professor Winn said.

OSHA Fines Dartmouth for Mercury Poisoning

The Occupational Safety and Health Administration (OSHA) of the U. S. Department of Labor has concluded its investigation into the death by mercury poisoning of a Dartmouth College professor. Federal regulators have fined Dartmouth College $13,500 for "serious" safety violations in connection with the death of Dr. Wetterhahn. A serious violation is defined by OSHA as one in which there is substantial probability that death or serious physical harm could result, and the employer knew or should have known of the hazard.

David May, OSHA's New Hampshire director, said Dartmouth had failed to provide adequate training on the limits of the gloves and to provide appropriate gloves for the research of dimethyl mercury. Also, the Lab's Chemical Hygiene Plan was fine for deficiencies.

Director May stressed dimethyl mercury is highly toxic with little commercial use. It was being used in research as an NMR standard. Dartmouth officials said they would not contest the fine and would comply with OSHA's safety recommendations. In the past months, the college has held workshops on different types of gloves and their uses, and has affixed labels to gloves warning of their limitations.

APPENDIX B.

OSHA HAZARD INFORMATION BULLETIN FOR: DIMETHYLMERCURY.

http://www.osha.gov/dts/hib/hib_data/hib19980309.html

U.S. Department of Labor
Occupational Safety & Health Administration
www.osha.gov

OSHA Hazard Information Bulletins
Hazard Information Bulletin for: Dimethylmercury.
Information Date: 19980309

March 9, 1998
MEMORANDUM FOR: REGIONAL ADMINSTRATORS
THROUGH: EMZELL BLANTON, JR.
Acting Deputy Assistant Secretary
FROM: STEVEN F. WITT Director
Directorate of Technical Support
SUBJECT: Hazard Information Bulletin* for: Dimethylmercury

The Boston Regional Office has brought to our attention the extreme toxicity of an organometallic chemical, dimethylmercury following the investigation of a fatal chemical exposure to a researcher. The death of a chemistry professor in June 1997 was apparently due to a single exposure to dimethylmercury.

Dimethylmercury belongs to a class of organic mercury compounds known as alkyl mercuries. It is used primarily in research. It is a colorless liquid described as having a weak, sweet odor. Dimethylmercury is readily absorbed through the skin. A severely toxic dose requires the absorption of less than 0.1mL.(1) Many materials, including several plastics and rubber compounds, have also been shown to be permeable to this chemical. It is highly reactive and flammable. Because of its high vapor pressure (50-82 mm Hg at 20°C), the inhalation route of entry is also significant.

Case Report

The exposure occurred when, during a transfer to another container, one to several drops of dimethylmercury were spilled on the back of the researcher's gloved left hand. The transfer was conducted under a fume hood and the researcher was wearing disposable latex gloves. Five months later the researcher experienced progressive difficulty characterized by numbness and tingling in both lower extremities, along with difficulty in vision, walking, speaking, and hearing. When informed that her symptoms were due to mercury poisoning, the spill incident was recalled and she indicated that she had removed the gloves promptly and did not think any

more about the incident. As a result, no medical monitoring or other follow-up was done until the diagnosis five months after the exposure.

Full diagnostic evaluation identified organometallic toxicity as a result of exposure to dimethylmercury as the cause. Hair analysis for mercury was consistent with a single or short exposure, such as the reported spill, and peaked at 54 days post exposure followed by subsequent slow decline in mercury levels. Mercury levels in hair are reflective of blood mercury levels at the time the hair was formed. Therefore, analysis of the levels versus time (hair length where sample was taken) can give a history of mercury exposure prior to when the problem was recognized. The mercury level in the urine was 234 µg/L; blood mercury level was 4,000 µg/L five months after the exposure (background levels in unexposed populations are 4-5 µg/L and 1-8 µg/L respectively). Despite aggressive chelation treatment, the patient went into a coma and died 10 months after exposure. Diagnosis at the time of death was encephalopathy as a result of mercury intoxication. The gloves used in this incident were disposable latex examination gloves and subsequent permeation testing of the gloves by a certified, independent testing laboratory indicated that the chemical permeates latex, PVC, and neoprene almost instantaneously.

In keeping with other reported cases, the delayed onset of symptoms is not completely understood, although the intense lipophilia of the compound may play a role. Estimates regarding the amount of exposure ranged from "one to several drops."

Recommendations

As a result of this lethal incident of dimethylmercury exposure, the following recommendations are made regarding the use of dimethylmercury:

* Individuals should consider the use of less hazardous substances unless dimethylmercury is specifically required. For example, a major use of dimethylmercury is to calibrate certain research equipment such as Nuclear Magnetic Resonance (NMR). Inorganic mercury salts reportedly can be substituted for most of these operations.(2)

* Employees must wear impervious gloves, a face shield a minimum of 8 inches in length, and work under a hood when handling this chemical. Latex, neoprene and butyl gloves do not provide suitable protection for direct contact with dimethylmercury (dimethylmercury migrates through plastics and rubber). Permeability tests have shown that Silver Shield laminate gloves are impermeable to dimethylmercury for at least 4 hours. The Silver Shield glove should be worn under an outer glove that would be resistant to abrasion and tears. The vial containing the dimethylmercury should be clamped and the contents drawn up by means of a glass syringe and cannula. Gloves should be removed and disposed of in a manner that precludes re-entry of this material back into the workplace and in accordance with the requirements of the State Hazardous Waste Regulatory Authority. All gloves that may have been in contact with dimethylmercury should be considered contaminated and not reused.

* Employees using organometallic compounds such as dimethylmercury must be trained and aware of the toxic properties of these materials. MSDSs must be read with the understanding that they may not provide adequate guidance on glove selection.

* Individuals should use precautions similar to those described in the "Prudent Practices in the Laboratory"(3). Additional information on this case can be found in Chemical and Engineering News(4).

* All spills of this material or even suspected contact must be reported immediately to the employer and medical attention sought as soon as possible. Because of the high vapor pressure, dimethyl mercury evaporates rapidly and nearby workers could be quickly exposed to levels above the PEL of 0.01mg/cu.m.(5)

* Emergency showers and eyewash facilities must be provided within the immediate work area for emergency use particularly to deal with eye or skin contact. Soap must also be available.

* Medical surveillance consisting of periodic blood and urine testing of all individuals who work with this chemical on a routine or frequent basis should be provided by a physician experienced in occupational medicine.

This tragedy highlights the need for research laboratories to develop a protective chemical hygiene plan which includes adequate guidance on the appropriate selection of personal protective equipment and engineering controls. Highly placed or very well qualified researchers should not be assumed to have adequate health and safety information. Research facilities should recognize that the nature of their work leads to diverse and often severe health hazards, and occupational health and safety must be proportionately pro-active.

This document should be distributed to all laboratories and trade organizations that either use or distribute NMR scanners.

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2. Zachs R. Scientific American 277:20, Sep. 1997.

3. Prudent Practices in the Laboratory, Sections 5C; 5D; Nat. Acad. Press 1995.

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5. Toriba TY, Clarkson TW, Nierenberg DW. "Letters: More on working with dimethylmercury," Chemical and Engineering News, June 16, 1997, p.6.

APPENDIX C.

MATERIAL SAFETY DATA SHEET ON DIMETHYLMERCURY FROM CHEMICAL SUPPLIER

{Michael Gochfeld commentary is indicated in brackets AND boldface}

NOTE: The OSHA Hazard Communication Standard 29 CFR 1910.1200 mandates the use of Material Safety Data Sheets (MDSDs) as part of worker training. The following provision is found at 29 CFR 1910.1200 (g)(5):

> The chemical manufacturer, importer, or employer preparing the material safety data sheet shall ensure that the information recorded accurately reflects the scientific evidence used in making the hazard determination. If the chemical manufacturer, importer or employer preparing the material safety data sheet becomes newly aware of any significant information regarding the hazards of a chemical, or ways to protect against the hazards, this new information shall be added to the material safety data sheet within three months. **{This was not done for DMHg}**

{The following information is abstracted from the MSDS supplied with the chemical}

SECTION I - - - - - - - - - CHEMICAL IDENTIFICATION
DIMETHYLMERCURY Dimethylmercury 95%

SECTION 3 - - - - - - - - - HAZARD IDENTIFICATION

LABEL PRECAUTIONARY STATEMENTS

FLAMMABLE (USA)	HIGHLY FLAMMABLE (EU)
HIGHLY TOXIC (USA)	TOXIC (EU)

May cause harm to the unborn child.

Very toxic by inhalation, in contact with skin and if swallowed.
Irritating to eyes, respiratory system, and skin. Neurological hazard.

Target Organ: Kidneys **{Actually the main target is the nervous system}**

Keep away from sources of ignition. No smoking.
In case of accident or if you feel unwell, seek medical advice immediately.

Take off immediately ALL contaminated clothing. Do not breathe fumes.

In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
Wear suitable protective clothing, gloves and eye/face protection.

SECTION 8 - - - - - - - EXPOSURE CONTROLS/PERSONAL PROTECTION

Compatible chemical-resistant gloves. **{Inadequate detail}**
Chemical safety goggles.
NIOSH/MSHA approved respirator. **{Inadequate detail}**
Use only in a chemical, fume hood.
Safety shower and eye bath.
use non-sparking tools.
Do not breathe vapor.
Do not get in eyes, on skin, on clothing.
Avoid prolonged, or repeated exposure.
Wash thoroughly after handling. **{or if any contact with liquid is suspected}**
Keep tightly closed.
Keep away from heat, sparks, and open flame.

APPENDIX D.

DIMETHYLMERCURY ENTRY FROM CATALOGUE (ALDRICH CHEMICAL)

{Dimethylmercury can be purchased for laboratory use. The following entry from a major chemical supplier, appeared AFTER the Wetterhahn fatality. Aside from "Highly Toxic," it does not provide adequate warning.—M. Gochfeld}

32,808-1 Dimethylmercury, 95% [593-74-8] (methylmercury) $(CH_3)_2Hg$ FW 230.66 mp -43° 10 g $146.80
bp 93-94°nD 1.5430 d2961 Fp42°F(5°C)Beil. 4,678 Merck Index 12,3299
FT-NMR 1(3),737CSI 481, D,6, R&S 1(2),3043dRTECS#OW3010000 *HIGHLY TOXIC FLAMMABLE LIQUID*

APPENDIX E

NIOSH POCKET GUIDE TO CHEMICAL HAZARDS

Mercury (organo) alkyl compounds (as Hg)	**CAS**
	RTECS
Synonyms & Trade Names Synonyms vary depending upon the specific (organo) alkyl mercury compound.	**DOT ID & Guide**

Exposure Limits	NIOSH REL: TWA 0.01 mg/m^3 ST 0.03 mg/m^3 [skin]
	OSHA PEL†: TWA 0.01 mg/m^3 C 0.04 mg/m^3
IDLH 2 mg/m^3 (as Hg) See: merc-hg	**Conversion**

Physical Description
Appearance and odor vary depending upon the specific (organo) alkyl mercury compound.

Properties vary depending upon the specific (organo) alkyl mercury compound.		

Incompatibilities & Reactivities
Strong oxidizers such as chlorine

Measurement Methods
None available
See: NMAM or OSHA Methods

Personal Protection & Sanitation	**First Aid** (See procedures)
Skin: Prevent skin contact Eyes: Prevent eye contact Wash skin: When contaminated Remove: When wet or contaminated Change: Daily Provide: Eyewash, Quick drench	Eye: Irrigate immediately Skin: Soap wash immediately Breathing: Respiratory support Swallow: Medical attention immediately

NIOSH POCKET GUIDE TO CHEMICAL HAZARDS, CONT'D.

Important additional information about respirator selection
Respirator Recommendations NIOSH/OSHA
Up to 0.1 mg/m^3: (APF = 10) Any supplied-air respirator
Up to 0.25 mg/m^3: (APF = 25) Any supplied-air respirator operated in a continuous-flow mode
Up to 0.5 mg/m^3: (APF = 50) Any supplied-air respirator that has a tight-fitting facepiece and is operated in a continuous-flow mode/(APF = 50) Any self-contained breathing apparatus with a full facepiece/(APF = 50) Any supplied-air respirator with a full facepiece
Up to 2 mg/m^3: (APF = 1000) Any supplied-air respirator operated in a pressure-demand or other positive-pressure mode
Emergency or planned entry into unknown concentrations or IDLH conditions: (APF = 10,000) Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode/(APF = 10,000) Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained positive-pressure breathing apparatus
Escape: Any appropriate escape-type, self-contained breathing apparatus

Exposure Routes inhalation, skin absorption, ingestion, skin and/or eye contact

Symptoms Paresthesia; ataxia, dysarthria; vision, hearing disturbance; spasticity, jerking limbs; dizziness; salivation; lacrimation (discharge of tears); nausea, vomiting, diarrhea, constipation; skin burns; emotional disturbance; kidney injury; possible teratogenic effects

Target Organs Eyes, skin, central nervous system, peripheral nervous system, kidneys

See also: INTRODUCTION See MEDICAL TESTS: 0135