INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 118

INORGANIC MERCURY

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Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

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World Health Orgnization
Geneva, 1991

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

    Every effort has been made to present information in
the criteria monographs as accurately as possible without
unduly delaying their publication. In the interest of all
users of the environmental health criteria monographs,
readers are kindly requested to communicate any errors
that may have occurred to the Manager of the International
Programme on Chemical Safety, World Health Organization,
Geneva, Switzerland, in order that they may be included in
corrigenda, which will appear in subsequent volumes.

*   *   *

    A detailed data profile and a legal file can be
obtained from the International Register of Potentially
Toxic Chemicals, Palais des Nations, 1211 Geneva 10,
Switzerland (Telephone No. 7988400 or 7985850).

ENVIRONMENTAL HEALTH CRITERIA FOR INORGANIC MERCURY

    A WHO Task Group on Environmental Health Criteria for
Inorganic Mercury met in Bologna, Italy, at the County
Council Headquarters (Provincia) from 25 to 30 September
1989. The meeting was sponsored by the Italian Ministry
of the Environment and organized locally by the Institute
of Oncology and Environmental Sciences with the assistance
of the County Council. Professor C. Maltoni, Director of
the Bologna Institute of Oncology, opened the meeting and
welcomed the participants on behalf of the host insti-
tution. Mr A. Vecchi, Dr M. Moruzzi, and Dr A. Lolli, wel-
comed the participants on behalf of the local authorities.
Dr A. Mochi, Centro Italiano Studi e Indagini, greeted the
participants on behalf of the Ministry of the Environment,
and Dr D. Kello, WHO Regional Office for Europe, addressed
the meeting on behalf of the cooperating organizations of
the IPCS (ILO/UNEP/WHO).

    The Task Group reviewed and revised the draft document
and made an evaluation of the human health risks from
exposure to inorganic mercury.

    The draft of this report was prepared by Dr L.
Friberg, Karolinska Institute, Stockholm, Sweden. Dr T.
Kjellström, WHO, Geneva, was responsible for the overall
scientific content and Dr P.G. Jenkins, WHO, Geneva, for
the technical editing.

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ABBREVIATIONS

AAS   atomic absorption spectrophotometry

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CNS        central nervous system

CVAA       cold vapour atomic absorption

EEC        European Economic Community

EEG        electroencephalogram

GBM        glomerular basement membrane

GC         gas chromatography

GEMS       Global Environment Monitoring System

GLC        gas-liquid chromatography

LOAEL      lowest-observed-adverse-effect level

MGP        membranous glomerulopathy

NOAEL      no-observed-adverse-effect level

SD         standard deviation

SMR        standardized mortality ratio

TWA        time-weighted average
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1. SUMMARY AND CONCLUSIONS

This monograph concentrates primarily on the risk to
human health from inorganic mercury, and examines research
reports that have appeared since the publication of
Environmental Health Criteria 1: Mercury (WHO, 1976). In
the period since 1976, new research data has become avail-
able for two main health concerns related to inorganic
mercury, i.e. mercury in dental amalgam and in skin-
lightening soaps. The emphasis in this monograph is on
exposure from these two sources, but the basic kinetics
and toxicology are reviewed with all aspects of inorganic
mercury in mind.

Human health concerns related to the global transport,
bioaccumulation, and transformation of inorganic mercury
almost exclusively arise from the conversion of mercury
compounds into methylmercury and exposure to methylmercury
in sea-food and other food. The global environmental and
ecological aspects of inorganic mercury have been summar-
ized in this monograph. More detailed descriptions may be
found in Environmental Health Criteria 86: Mercury -
Environmental Aspects (WHO, 1989) and Environmental Health
Criteria 101: Methylmercury (WHO, 1990).

1.1. Identity

Mercury exists in three states: Hg^0 (metallic);

Hg_2^{++} (mercurous); and Hg^{++} (mercuric). It can form organometallic compounds, some of which have found industrial and agricultural uses.

1.2. Physical and chemical properties

Elemental mercury has a very high vapour pressure. The saturated atmosphere at 20 °C has a concentration over 200 times greater than the currently accepted concentration for occupational exposure.

Solubility in water increases in the order: elemental mercury < mercurous chloride < methylmercury chloride < mercuric chloride. Elemental mercury and the halide compounds of alkylmercurials are soluble in non-polar solvents.

Mercury vapour is more soluble in plasma, whole blood, and haemoglobin than in distilled water, where it dissolves only slightly. The organometallic compounds are stable, although some are readily broken down by living organisms.

1.3. Analytical methods

The most commonly used analytical methods for the quantification of total and inorganic mercury compounds are atomic absorption of cold vapour (CVAA) and neutron

activation. Detailed information relating to analytical methods are given in Environmental Health Criteria 1: Mercury (WHO, 1976) and Environmental Health Criteria 101: Methylmercury (WHO, 1990).

All analytical procedures for mercury require careful quality control and quality assurance.

1.3.1. Analysis, sampling, and storage of urine

Flameless atomic absorption spectrophotometry is used in routine analysis for various media. Particular care must be taken when choosing the anticoagulant used for blood sampling in order to avoid contamination by mercury compounds. Special care must also be taken in the sampling and storage of urine, since bacterial growth can change the concentration of the numerous forms of mercury that may be present. Addition of hydrochloric acid or bactericidal substances and freezing the sample are the best methods to prevent alteration of urine samples. Correction of concentration by reference to urine density or creatinine content are recommended.

1.3.2. Analysis and sampling of air

Analytical methods for mercury in air may be divided into instant reading methods and methods with separate sampling and analysis stages. Instant reading methods can

be used for the quantification of elemental mercury vapour. Sampling in acid-oxidizing media or on hopcalite is used for the quantification of total mercury.

The cold vapour atomic absorption (CVAA) technique is the most frequently used analytical method.

1.4. Sources of human and environmental exposure

1.4.1. Natural occurrence

The major natural sources of mercury are degassing of the earth's crust, emissions from volcanoes, and evaporation from natural bodies of water.

The natural emissions are of the order of 2700-6000 tonnes per year.

1.4.2. Sources due to human activities

The world-wide mining of mercury is estimated to yield about 10 000 tonnes/year. These activities lead to some losses of mercury and direct discharges to the atmosphere. Other important sources are fossil fuel combustion, metal sulfide ore smelting, gold refining, cement production, refuse incineration, and industrial applications of metals.

The specific normal emission from a chloralkali plant is about 450 g of mercury per ton of caustic soda produced.

The total global amount and release of mercury, due to human activities, to the atmosphere has been estimated to be up to 3000 tonnes/year.

1.5. Uses

A major use of mercury is as a cathode in the electrolysis of sodium chloride. Since the resultant chemicals are contaminated with mercury, their use in other industrial activities leads to a contamination of other products. Mercury is used in the electrical industry, in control instruments in the home and industry, and in laboratory and medical instruments. Some therapeutic agents contain inorganic mercury. A very large amount of mercury is used for the extraction of gold.

Dental silver amalgam for tooth filling contains large amounts of mercury, mixed (in the proportion of 1:1) with alloy powder (silver, tin, copper, zinc). Copper amalgam, used mostly in paediatric dentistry, contains up to 70% mercury and up to 30% copper. These uses can cause exposure of the dentist, dental assistants, and also of the patients.

Some dark-skinned people use mercury-containing creams

and soap to achieve a lighter skin tone. The distribution of these products is now banned in the EEC, in North America, and in many African countries, but mercury-containing soap is still manufactured in several European countries. The soaps contain up to 3% of mercuric iodine and the creams contain ammoniated mercury (up to 10%).

1.6. Environmental transport, distribution, and transformation

Emitted mercury vapour is converted to soluble forms and deposited by rain onto soil and water. The atmospheric residence time for mercury vapour is up to 3 years, whereas soluble forms have a residence time of only a few weeks.

The change in speciation of mercury from inorganic to methylated forms is the first step in the aquatic bioaccumulation process. This can occur non-enzymically or through microbial action. Methylmercury enters the food-chain of predatory species where biomagnification occurs.

1.7. Human exposure

The general population is primarily exposed to mercury through the diet and dental amalgam. Depending on the concentrations in air and water, significant contributions to

the daily intake of total mercury can occur. Fish is a dominant source of human exposure to methylmercury. Recent experimental studies have shown that mercury is released from amalgam restorations in the mouth as vapour. The release rate of this mercury vapour is increased, for example, by chewing. Several studies have correlated the number of dental amalgam fillings or amalgam surfaces with the mercury content in tissues from human autopsy, as well as in samples of blood, urine, and plasma. Both the predicted mercury uptake from amalgam and the observed accumulation of mercury show substantial individual variation. It is, therefore, difficult to make accurate quantitative estimations of the mercury release and uptake by the human body from dental amalgam tooth restorations. Experimental studies in sheep have examined in greater detail the distribution of mercury released from amalgam restorations.

Use of skin-lightening soap and creams can give rise to substantial mercury exposure.

Occupational exposure to inorganic mercury has been investigated in chloralkali plants, mercury mines, thermometer factories, refineries, and in dental clinics. High mercury levels have been reported for all these occupational exposure situations, although levels vary according to work environment conditions.

1.8. Kinetics and metabolism

Results of both human and animal studies indicate that about 80% of inhaled metallic mercury vapour is retained by the body, whereas liquid metallic mercury is poorly absorbed via the gastrointestinal tract (less than 1%). Inhaled inorganic mercury aerosols are deposited in the respiratory tract and absorbed, the rate depending on particle size. Inorganic mercury compounds are probably absorbed from the human gastrointestinal tract to a level of less than 10% on average, but there is considerable individual variation. Absorption is much higher in newborn rats.

The kidney is the main depository of mercury after the administration of elemental mercury vapour or inorganic mercury compounds (50-90% of the body burden of animals). Significantly more mercury is transported to the brain of mice and monkeys after the inhalation of elemental mercury than after the intravenous injection of equivalent doses of the mercuric form. The red blood cell to plasma ratio in humans is higher ($\geq$ 1) after administration of elemental mercury than mercuric mercury and more mercury crosses the placental barrier. Only a small fraction of the administered divalent mercury enters the rat fetus.

Several forms of metabolic transformation can occur:

*   oxidation of metallic mercury to divalent mercury;
*   reduction of divalent mercury to metallic mercury;
*   methylation of inorganic mercury;
*   conversion of methylmercury to divalent inorganic mercury.

The oxidation of metallic mercury vapour to divalent ionic mercury (section 6.1.1) is not fast enough to prevent the passage of elemental mercury through the blood-brain barrier, the placenta, and other tissues. Oxidation in these tissues serves as a trap to hold the mercury and leads to accumulation in brain and fetal tissues.

The reduction of divalent mercury to Hg^0 has been demonstrated both in animals (mice and rats) and humans. The decomposition of organomercurials, including methyl-mercury, is also a source of mercuric mercury.

The faecal and urinary routes are the main pathways for the elimination of inorganic mercury in humans, although some elemental mercury is exhaled. One form of depletion is the transfer of maternal mercury to the fetus.

The biological half-time, which only lasts a few days or weeks for most of the absorbed mercury, is very long, probably years, for a fraction of the mercury. Such long half-times have been observed in animal experiments as well as in humans. A complicated interplay exists between mercury and some other elements, including selenium. The formation of a selenium complex may be responsible for the

long half-time of a fraction of the mercury.

1.8.1. Reference and normal values

Limited information from deceased miners shows mercury concentrations in the brain, years after cessation of exposure, of several mg/kg, with still higher values in some parts of the brain. However, lack of quality control of the analysis makes these data uncertain. Among a small number of deceased dentists, without known symptoms of mercury intoxication, mercury levels varied from very low concentrations up to a few hundred µg/kg in the occipital lobe cortex and from about 100 µg/kg to a few mg/kg in the pituitary gland.

From autopsies on subjects not occupationally exposed but with a varying number of amalgam fillings, it seems that a moderate number (about 25) of amalgam surfaces may on average increase the brain mercury concentration by about 10 µg/kg. The corresponding increase in the kidneys, based on a very limited number of analyses, is probably 300-400 µg/kg. However, the individual variation is considerable.

Mercury levels in urine and blood can be used as indicators of exposure provided that the exposure is recent and relatively constant, is long-term, and is evaluated on a group basis. Recent exposure data are more reliable than those quoted in Environmental Health Criteria 1: Mercury (WHO, 1976). Urinary levels of about 50 µg per g creatinine are seen after occupational exposure to about 40 µg mercury/m^3 of air. This relationship (5:4) between urine and air levels is much lower that the 3:1 estimated by WHO (1976). The difference may in part be explained by different sampling technique for evaluating air exposure. An exposure of 40 µg mercury/m^3 of air will correspond to about 15-20 µg mercury/litre of blood. However, interference from methylmercury exposure can make it difficult to evaluate exposure to low concentrations of inorganic mercury by means of blood analysis. A way to overcome the problems is to analyse mercury in plasma or analyse both inorganic mercury and methylmercury. The problem of interference from methylmercury is much smaller when analysing urine, as methylmercury is excreted in the urine to only a very limited extent.

1.9. Effects in humans

Acute inhalation exposure to mercury vapour may be followed by chest pains, dyspnoea, coughing, haemoptysis, and sometimes interstitial pneumonitis leading to death. The ingestion of mercuric compounds, in particular mercuric chloride, has caused ulcerative gastroenteritis and acute tubular necrosis causing death from anuria where dialysis was not available.

The central nervous system is the critical organ for

mercury vapour exposure. Subacute exposure has given rise
to psychotic reactions characterized by delirium, halluci-
nations, and suicidal tendency. Occupational exposure has
resulted in erethism as the principal feature of a broad
ranging functional disturbance. With continuing exposure a
fine tremor develops, initially involving the hands. In
the milder cases erethism and tremor regress slowly over a
period of years following removal from exposure. De-
creased nerve conduction velocity has been demonstrated in
mercury-exposed workers.   Long-term, low-level exposure
has been associated with less pronounced symptoms of
erethism.

    There is very little information available on brain
mercury levels in cases of mercury poisoning, and nothing
that makes it possible to estimate a no-observed-effect
level or a dose-response curve.

    At a urinary mercury excretion level of 100 µg per g
creatinine, the probability of developing the classical
neurological signs of mercurial intoxication (tremor,

erethism) and proteinuria is high. An exposure correspond-
ing to 30 to 100 µg mercury/g creatinine increases the
incidence of some less severe toxic effects that do not
lead to overt clinical impairment. In a few studies
tremor, recorded electrophysiologically, has been observed
at low urine concentrations (down to 25-35 µg/g creati-
nine). Other studies did not show such an effect. Some of
the exposed people develop proteinuria (proteins of low
relative molecular mass and microalbuminuria). Appropriate
epidemiological data covering exposure levels correspond-
ing to less than 30-50 µg mercury/g creatinine are not
available.

    The exposure of the general population is generally
low, but may occasionally be raised to the level of occu-
pational exposure and can even be toxic. Thus, the
mishandling of liquid mercury has resulted in severe
intoxication.

    The kidney is the critical organ following the
ingestion of inorganic divalent mercury salts. Occu-
pational exposure to metallic mercury has long been
associated with the development of proteinuria, both in
workers with other evidence of mercury poisoning and in
those without such evidence. Less commonly, occupational
exposure has been followed by the nephrotic syndrome,
which has also occurred after the use of skin-lightening
creams containing inorganic mercury, and even after acci-
dental exposure. The current evidence suggests that this
nephrotic syndrome results from an immunotoxic response.
Until recently, effects of elemental mercury vapour on the
kidney had been reported only at doses higher than those
associated with the onset of signs and symptoms from the
central nervous system. New studies have, however, re-
ported kidney effects at lower exposure levels. Experi-

mental studies on animals have shown that inorganic mercury may induce auto-immune glomerulonephritis in all species tested, but not in all strains, indicating a genetic predisposition. A consequence of an immunological etiology is that, in the absence of dose-response studies for groups of immunologically sensitive individuals, it is not scientifically possible to set a level for mercury (e.g., in blood or urine) below which (in individual cases) mercury-related symptoms will not occur.

Both metallic mercury vapour and mercury compounds have given rise to contact dermatitis. Mercurial pharmaceuticals have been responsible for Pink disease in children, and mercury vapour exposure may be a cause of "Kawasaki" disease. In some studies, but not in others, effects on the menstrual cycle and/or fetal development have been reported. The standard of published epidemiological studies is such that it remains an open question whether mercury vapour can adversely affect the menstrual

cycle or fetal development in the absence of the well-known signs of mercury intoxication.

Recently, there has been an intense debate on the safety of dental amalgams and claims have been made that mercury from amalgam may cause severe health hazards. Reports describing different types of symptoms and signs and the results of the few epidemiological studies produced are inconclusive.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1. Identity

This monograph focuses on the risk to human health from the compounds of inorganic mercury. Other forms of mercury are discussed where they are relevant to the full evaluation of human health risks, e.g., the metabolic transformation of methylmercury to inorganic mercury.

Elemental mercury has the CAS registry number 7439-97-6 and a relative atomic mass of 200.59. There are three states of inorganic mercury: Hg^0 (metallic), Hg_2^{++} (mercurous), and Hg^{++} (mercuric) mercury. The mercurous and mercuric states form numerous inorganic and organic chemical compounds. Organic forms are those in which mercury is attached covalently to at least one carbon atom.

2.2. Physical and chemical properties

In its elemental form, mercury is a heavy silvery liquid at room temperature. At 20 °C the specific gravity of the metal is 13.456 and the vapour pressure is 0.16 Pa (0.0012 mmHg). Thus, a saturated atmosphere at 20 °C contains approximately 15 mg/m^3. This concentration is 300 times greater than the recommended health-based occu-

pational exposure limit of 0.05 mg/m^3 (WHO, 1980).

Mercurials differ greatly in their solubilities. Solubility values in water are: elemental mercury (30 °C), 2 µg/litre; mercurous chloride (25 °C), 2 mg/litre; mercuric chloride (20 °C), 69 g/litre (Linke, 1958; CRC, 1972). The solubility of methylmercury chloride in water is higher than that of mercurous chloride by about three orders of magnitude, this being related to the very high solubility of the methylmercury cation in water (Linke, 1958; Clarkson et al., 1988b). Certain species of mercury are soluble in non-polar solvents. These include elemental mercury and the halide compounds of alkylmercurials (Clarkson et al., 1988b).

From the biochemical point of view the most important chemical property of mercuric mercury and alkylmercurials is their high affinity for sulfhydryl groups.

Hursh (1985) showed that mercury vapour is more soluble in plasma, whole blood, and haemoglobin than in distilled water or isotonic saline.

The following speciation among mercury compounds has been proposed by Lindqvist et al. (1984), where V indicates volatile species, R water-soluble particle-borne

reactive species, and NR non-reactive species:

V: Hg^0 (elemental mercury), $(CH_3)_2Hg$

R: Hg^{2+}, HgX_2, HgX_3^-, and HgX_4^{2-} (where X = OH^-, Cl^-, or Br^-), Hg^0 on aerosol particles, Hg^{2+} complexes with organic acids.

NR: CH_3Hg^+, CH_3HgCl, CH_3HgOH, and other organomercuric compounds, $Hg(CN)_2$, HgS, and Hg^{2+} bound to sulfur in fragments of humic matter.

The main volatile form in air is elemental mercury, but dimethylmercury may also occur (Slemr et al., 1981).

Uncharged complexes, such as $HgCl_2$ and CH_3HgOH, occur in the gaseous phase, but are also relatively stable in fresh water (snow and rain as well as standing or flowing water). $HgCl_4^{2-}$ is the dominant form in sea water.

2.3. Conversion factors

1 ppm = 1 mg/kg = 5 µmol/kg
1 mol creatinine = 113.1 g creatinine

2.4. Analytical methods

Detailed information relating to analytical methods was given in Environmental Health Criteria 1: Mercury (WHO, 1976) and in Environmental Health Criteria 101:

Methylmercury (WHO, 1990). This monograph contains further information concerning the sampling and analysis of urine and air, the most frequently studied media for evaluation of exposure to inorganic mercury. A summary of the commonly used analytical methods is given in Table 1. More advanced methods, such as inductively coupled plasma atomic emission spectrometry and spark source mass spectrometry, are described in Kneip & Friberg (1986).

2.4.1. Analysis, sampling, and storage of urine

For routine analysis, various forms of flameless atomic absorption spectrophotometry (AAS) are used. The "Magos" selective atomic absorption method determines both total and inorganic mercury and, by difference, organic mercury. The neutron activation procedure is regarded as the most accurate and sensitive procedure and is usually used as the reference method.

Table 1. Analytical methods for the determination of mercury

Media References	Speciation	Analytical method	Detection limit (ng Hg/g)	Comments
Food, tissues many adaptations Hatch & Ott (1968) & Strunc, 1984)	total mercury	atomic absorption	2.0	method has (see Peter
Blood, urine estimates organic mercury Magos (1971); Magos & Clarkson (1972) difference between total inorganic	total mercury inorganic mercury	atomic absorption	0.5	also as and
Blood, urine form of the method Farant et al. (1981) hair, tissues (1971)	total mercury inorganic mercury	atomic absorption	2.5	automated of Magos
Blood, urine form of the method Coyle & Hartley (1981) hair, tissues (1971)	total mercury inorganic mercury	atomic absorption	4.0	automated of Magos
All media method (review) WHO (1976)	total mercury	neutron activation	0.1	reference

Blood samples are best collected in "vacutainers"

containing heparin (without mercury compounds as preservative) (WHO, 1980) and stored at 4 °C prior to analysis. This method of collection is especially important if mercury levels in plasma and red blood cells are to be measured. Blood samples can usually be stored for one or two days before haemolysis becomes significant (Clarkson et al., 1988c).

The sampling and storage of urine have been discussed in detail by Clarkson et al. (1988c). It is important to avoid contamination of urine samples; special cleaning procedures and the use of metal-free polyethylene containers have been recommended.

As a rule, urine is saturated with several inorganic salts. Precipitates are sometimes seen in freshly voided samples and are normally present in urine samples that have been stored at low temperature (1-4 °C). To lessen problems of precipitates, urine samples should be homogenized by shaking before analysis. Alternatively, a strong acid, preferably hydrochloric acid, can be added to the urine sample to lower pH and increase the solubility of the salts.

Bacterial growth is rapid in urine at room temperature. Even urine samples from healthy people become overgrown with bacteria after only a few hours. If urine samples are frozen (to below -20 °C), bacterial growth is reduced substantially. Bacteria may reduce some mercury compounds to elemental mercury, which might give rise to significant losses of mercury by volatilization (WHO, 1976). Bactericidal substances, such as sodium azide, may be added to urine samples. However, sodium azide is a strong reducing agent and may form Hg^0 from Hg^{2+}. The addition of 1 g sulfamic acid and 0.5 ml of a detergent (Triton X-100) to 500 ml of urine produces stable urine samples at room temperature for at least one month (Skare, 1972).

Even when the rate of metal excretion is constant, metal concentration in urine varies according to the urine flow rate (Diamond, 1988). It is therefore necessary to adjust the measured concentrations of metals in spot urine samples for variations in the urine flow rate. This can be done by correcting for urine relative density or osmolality or by dividing by the concentration of creatinine in the urine sample. Another alternative is the use of timed urine specimens (e.g., 4 h or 8 h). If the concentration of a substance is standardized to a constant relative density (usually 1.018 or 1.024), the basis of correction chosen profoundly changes the figures obtained. Correction to 1.024 gives values 33% higher than correction to 1.018 (Aitio, 1988). Furthermore, many chemicals,

including mercury, exhibit diurnal variation in concentration (Piotrowski et al., 1975). Correction using creatinine values has the advantage that the mercury concen-

tration will be independent of hydration status.

2.4.2. Analysis and sampling of air

Analytical methods for mercury in air may be divided into instant reading methods and methods with separate sampling and analysis stages (WHO, 1976).

One instant reading method is based on the "cold vapour atomic absorption" (CVAA) technique, which measures the absorption of mercury vapour by ultra-violet light using a wave length of 253.7 nm. Most of the AAS procedures have a detection limit in the range of 2 to 5 µg mercury/m^3.

Another instant reading method that has been used increasingly in recent years is a special type of gold amalgamation technique. This method has been used in a number of studies for evaluating the release of elemental mercury vapour in the oral cavity from amalgam fillings (Svare et al., 1981; Vimy & Lorscheider, 1985a,b). McNerney et al. (1972) gave a detailed description of the method, which is based on an increase in the electrical resistance of a thin gold film after adsorption of mercury vapour. The detection limit is 0.05 ng mercury. Within the range of 0.5 to 25 ng, the relative standard deviation was found to vary between 3 and 10% when 15 samples from each of 6 mercury vapour standards were examined. At higher mercury concentrations, the films become saturated with mercury and precision decreases. It is possible to correct for this saturation with a calibration curve. However, there are no data on the accuracy of the method when used in actual field studies, such as the ones by Svare et al. (1981) or Vimy & Lorscheider (1985a,b).

In an analytical method based on separate sampling and analysis, the air is sampled in two bubblers in series, containing sulfuric acid and potassium permanganate (WHO, 1976). The mercury is subsequently determined by CVAA. With this method the *total* mercury in the air is measured, not just mercury vapour. Another sampling technique uses solid absorbants. Different amalgamation techniques using gold have been shown to have good collection efficiency for mercury vapour (McCammon et al., 1980; Dumarey et al., 1985; Skare & Engqvist, 1986). Roels et al. (1987) used a filter with two layers of hopcalite (a mixture of metal oxides that can absorb metals) to collect the mercury. After solubilization, the mercury was analysed by a CVAA technique. It was necessary also to measure blanks of hopcalite and scrubbing solution. Large variations were found for background mercury contamination of hopcalite from batch to batch (6-93 ng mercury per 200 mg hopcalite).

Sampling of air for mercury analysis can be made by static samplers or by personal monitoring. Personal samplers are recommended. A study by Roels et al. (1987) compared results obtained with the use of static samplers

with results from personal samplers. In most of the
workplaces, personal samplers yielded higher exposure
levels (time-weighted averages) than did static samplers
(see section 6.5.2).

2.4.3. Quality control and quality assurance

General considerations of quality control and quality
assurance have been recommended by WHO (UNEP/WHO, 1984;
WHO, 1986; Aitio, 1988). At a recent conference on "Bio-
logical Monitoring of Toxic Metals" (Friberg, 1988), a
WHO approach based on a GEMS programme (Vahter, 1982) was
described in detail. Specific quality control programmes
for mercury in hair using the GEMS approach have been
described (Lind et al., 1988). Roels et al. (1987) suc-
cessfully used another regression method when analysing
mercury in urine.

In almost any quality control programme, there is a
need for reference materials containing the metal in con-
centrations covering the expected working range of moni-
toring samples. Several reference materials are commer-
cially available for both environmental samples and for
urine and blood (Muramatsu & Parr, 1985; Parr et al.,
1987; Rasberry, 1987; Parr et al., 1988; Okamoto, 1988).
The following are suppliers of reference materials: NIST
(Office of Standard Reference Materials, National Insti-
tute of Standards and Technology, Rm. B311, Chemistry
Bldg., Gaithersburg, MD 20899, USA), IAEA (International
Atomic Energy Agency, Analytical Quality Control Services,
Laboratory Seibersdorf, A-1400 Vienna), BCR (Community
Bureau of Reference, Commission of the European Communi-
ties, 200 Rue de la Loi, B-1049 Brussels, Belgium); NIES
(National Institute for Environmental Studies, Japan
Environment Agency, P.O. Yatabe, Tsukuba Ibaraki 300-21,
Japan), NRCC (National Research Council Canada, Division
of Chemistry, Ottawa, K1A OR6, Canada), Nycomed AS Diag-
nostics (P.O. Box 4220, Torshov, 0401 Oslo 4, Norway),
Behring Institute (P.O. Box 1140, D-3550 Marburg 1,
Germany), Kaulson Laboratories Inc. (691 Bloomfield
Avenue, Caldwell, New Jersey 07006, USA). However, the
available reference materials do not cover the demand for
different mercury species, biological media or for differ-
ent concentrations. Only NRCC has a reference material
(fish) for total mercury and for methylmercury.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1. Natural occurrence

The major natural sources of mercury are the degassing
of the earth's crust, emissions from volcanoes, and evap-
oration from natural bodies of water (National Academy of
Sciences, 1978; Nriagu, 1979; Lindqvist et al., 1984). The
most recent estimates indicate that natural emissions are
of the order of 2700-6000 tonnes per year (Lindberg et
al., 1987).

The earth's crust is also an important source of mercury for bodies of natural water. Some of this mercury is undoubtedly of natural origin, but some may have been deposited from the atmosphere and may ultimately have been generated by human activities (Lindqvist et al., 1984). Thus, it is difficult to assess quantitatively the relative contributions of natural and anthropogenic mercury to run-off from land to natural bodies of water. Data concerning mercury in the general environment and in food have been reviewed in Environmental Health Criteria 101: Methylmercury (WHO, 1990).

3.2. Man-made sources

The worldwide mining of mercury is estimated to yield about 10 000 tonnes/year. Mining activities result in losses of mercury through the dumping of mine tailings and direct discharges to the atmosphere. The Almaden mercury mine in Spain, which accounts for 90% of the total output of the European Community, was expected to produce 1380 tonnes in 1987 (Seco, 1987). Other important sources are the combustion of fossil fuel, the smelting of metal sulfide ores, the refining of gold (sometimes under very primitive conditions), the production of cement, refuse incineration, and industrial metal applications. The emissions of mercury to the atmosphere in Sweden in 1984 were estimated to be as follows (in kg/year): incineration of household waste (3300), smelting (900), chloralkali industry (400), crematories (300), mining (200), combustion of coal and peat (200), other sources (200) (Swedish Environmental Protection Board, 1986). Analogous data for the estimated atmospheric emissions of mercury in the United Kingdom were (in kg/year): fossil fuel combustion (25 500), production and use of articles containing mercury (10 100), municipal waste incineration (5900), non-ferrous metal production (5000), cement manufacture (2500), iron and steel production (1800), sewage sludge incineration (500) (Dean & Suess, 1985). In developing countries the emissions from industry and mining may be much greater. For example, the emission to water from one single chloralkali plant in Nicaragua in 1980 was 24 kg per day (9 tonnes/year) (Velasquez et al., 1980). It was estimated that 450 g of mercury was emitted per tonne of

soda produced in six chloroalkali plants in Argentina, and the quantity of mercury released in the environment was about 86 tonnes/year (Gotelli, 1989).

The total global release of mercury to the atmosphere due to human activities has been estimated to be of the order of 2000-3000 tonnes/year (Lindberg et al., 1987; Pacyna, 1987). It should be stressed that there are considerable uncertainties in the estimated fluxes of mercury in the environment and in its speciation. Concentrations in the unpolluted atmosphere and in natural bodies of water are so low that they are near the limit of detection

of current analytical methods, even for the determination of total mercury.

Although amounts of mercury resulting from human activities may be quite small relative to global emissions, the anthropogenic release of elemental metal mercury into confined areas was the source of the poisoning outbreaks in Minamata and Niigata (WHO, 1976).

3.3. Uses

A major use of mercury is as a cathode in the electrolysis of sodium chloride solution to produce caustic soda and chlorine gas, which has important uses in the paper-pulp industry. It should be noted that all the electrolytic products (hydrogen, chlorine, sodium hydroxide, sodium hypochlorite, and hydrochloric acid) are contaminated with mercury (Gotelli, 1989). These substances are important in the economy of other industrial activities and the presence of mercury can contaminate other products. About 50 tonnes of liquid metal are used in each manufacturing plant. In most industrialized countries, stringent procedures have been taken to reduce losses of mercury. Mercury is widely used in the electrical industry (lamps, arc rectifiers, and mercury battery cells), in control instruments in the home and industry (switches, thermostats, barometers), and in other laboratory and medical instruments. It is also widely used in the dental profession for tooth amalgam fillings. Other therapeutic agents, such as teething powders, ointments, and laxatives, contain inorganic mercury (ATSDR, 1989), as do some antihistaminic preparations sold in Italy (EDIMED, 1989). Organic mercury compounds continue to be used in antifouling and mildew-proofing latex paints and to control fungus infections of seeds, bulb plants, and vegetation. The World Health Organization has warned against the use of alkylmercury compounds in seed dressing (WHO, 1976).

One of the uses of liquid metallic mercury that may have a serious impact on health is the extraction of gold from ore concentrates or from recycled gold articles. Reports from China (Wu et al., 1989) indicate high exposure in the vicinity of "cottage industry" operations

of this type, and Villaluz (1988) reported that 50 000 people may be exposed around small scale gold mining operations in Indonesia, Kampuchea, the Philippines, and Viet Nam. The same problem also occurs in Brazil and Colombia. The release of elemental mercury from these activities is about 120 tonnes/year in Brazil (Gotelli, 1989).

3.4. Dental amalgam in dentistry

WHO (1976) estimated that in industrial countries about 3% of the total consumption of mercury was used for dental amalgam. Amalgam has been used extensively as a

tooth-filling material for more than 150 years and accounts for 75-80% of all single tooth restorations (Bauer & First, 1982; Wolff et al., 1983). It has been estimated that each American dentist in private practice uses on average 0.9-1.4 kg of amalgam per year (Naleway et al., 1985).

Most conventional silver amalgams consist of a 1:1 mixture of metallic mercury and an alloy powder consisting of silver (about 70% by weight), tin (about 25%), and smaller amounts of copper (1-6%) and zinc (0-2%). A modern type of silver amalgam is also available, containing higher amounts of copper (up to about 25%). At the time of trituration (mixing), the amalgam generally contains similar weights of alloy powders and mercury. Excess mercury (< 5%) is removed immediately before or at the condensation of the plastic amalgam mix in the prepared tooth cavity. The amalgam begins to set within minutes of insertion and therefore needs to be carved to satisfactory anatomic form within this period of time. Finishing (e.g., polishing) with rotating instruments can take place after setting for 24 h, but continuing hardening of amalgam restorations takes place over many months (ADA, 1985; Enwonwu, 1987; SOS, 1987).

Previously, amalgam was usually prepared with mortar and pestle. The amalgam mixture was thereafter placed on a cloth filter and squeezed to expel excess mercury. This method of handling amalgam easily vapourizes mercury and there is also a risk of spillage. The technique is still in use in some countries (section 9.5.2.2). The modern, safer method for the preparation of amalgam involves mixing the alloy with mercury in a sealed capsule. This decreases the occupational exposure substantially (Harris et al., 1978; Skuba, 1984).

A second type of dental amalgam is the so-called "copper amalgam" used mostly in paediatric dentistry until a few decades ago. This material contained 60-70% mercury and 30-40% copper, and was prepared by open heating in the dental surgery. This process naturally gave rise to considerable occupational mercury vapour exposure.

Copper amalgams were easier to retain in dental cavities because of their higher initial plasticity than silver amalgams. Contrary to silver amalgam fillings, copper amalgam undergoes easily detectable dissolution with time. This solubilization was, for some time, actually considered an advantage because of the associated bactericidal effects (SOS, 1987).

A source of mercury loss to the atmosphere is the release of metallic mercury vapour during the cremation of cadavers. Crematories are often located in densely populated areas and do not have high chimneys. All the mercury from amalgam fillings vapourizes during the cremation, as the temperature is above 800 °C. In a Swedish study, it

has been estimated that 170-180 kg of metallic mercury is released annually from a total of about 50 000 cremations per year (Mörner & Nilsson, 1986). The use of amalgam in Sweden is estimated to be 5-7.5 tonnes per year (SOS, 1987), compared with 90-100 tonnes in the USA (Wolff et al., 1983; Naleway et al., 1985). It is difficult to estimate the global release of mercury vapour from cremation due to uncertainties about dental status at the time of death in relation to frequency of cremations.

3.5. Mercury-containing cream and soap

Mercury-containing cream and soap has for a long time been used by dark-skinned people to obtain a lighter skin tone, probably due to inhibition of pigment formation. There are mainly two types of products distributed for this purpose: skin-lightening creams and skin-lightening soaps. This subject has recently been reviewed by Berlin (personal communication to the IPCS by M. Berlin).

The distribution of the two products is now banned in the European Economic Community, in North America, and in many African states. Mercury-containing soap is, however, manufactured in several European countries and sold as germicidal soap to the Third World, and it has frequently been found in European cities with a substantial black population, such as London and Brussels. This implies that the mercury-containing soap manufactured in Europe has been re-imported illegally from African countries.

English community health authorities (Lambeth, 1988) have identified several brands of soap containing mercury. The soaps have been analysed and contain typically 1-3% of mercuric iodide. There are also skin-lightening creams containing ammoniated mercury from 1-5% (Marzulli & Brown, 1972) or 5-10% (Barr et al., 1973). Both the soap and the cream are applied on the skin, allowed to dry on the skin surface, and left overnight.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

There is a well-recognized global cycle for mercury, whereby emitted mercury vapour is converted to soluble forms (e.g., Hg^{++}) and deposited by rain onto soil and water. Mercury vapour has an atmospheric residence time of between 0.4 and 3 years, whereas soluble forms have residence times of a few weeks. Transport in soil and water is thus limited and deposition within a short distance is highly likely.

The change in mercury speciation from inorganic to methylated forms is the first step in the aquatic bioaccumulation process. Methylation can occur non-enzymatically or through microbial action. Once methylmercury is released, it enters the food chain by rapid diffusion and tight binding to proteins. It attains its highest levels, through food-chain biomagnification, in the tissues of

such predatory species as freshwater trout, pike, and bass and marine tuna, swordfish, and shark. The ratio of the methylmercury concentration in fish tissue to the concentration of inorganic mercury in water is usually between 10 000 and 100 000 to one. Levels of selenium in the water may affect the availability of mercury for uptake into aquatic biota. Reports from Sweden and Canada point to the likelihood of increased methylmercury concentration in fish after the construction of artificial water reservoirs (WHO, 1990).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

The general population is primarily exposed to mercury from dental amalgam and the diet. However, depending upon the level of contamination, air and water can contribute significantly to the daily intake of total mercury. In most foodstuffs, mercury is usually in the inorganic form and below the limit of detection (20 ng mercury/g fresh weight). The exceptions are fish and fish products, which are the main source of methylmercury in the diet. Levels greater than 1.2 mg/kg are often found in the edible portion of shark, swordfish, and Mediterranean tuna. Similar levels in pike, walleye, and bass taken from polluted fresh water have been identified. Table 2 indicates the average daily intake and retention of total mercury and mercury compounds in the general population not occupationally exposed to mercury.

The level of mercury in fish, even for humans consuming small amounts (10-30 g of fish/day), can markedly affect the intake of methylmercury and, thus, of total mercury. The weekly consumption of 200 g of fish having 500 µg mercury/kg will result in the intake of 100 µg mercury (predominantly methylmercury). This amount is one-half of the tolerable recommended weekly intake (WHO, 1989).

The subject of human mercury dietary exposure has been discussed in previous Environmental Health Criteria monographs (WHO, 1976, 1990). This section emphasizes human exposure to inorganic mercury from dental amalgam and skin-lightening creams and soaps among the general population, and occupational exposure due to the use of amalgam in dentistry. Industrial exposure was described in detail in WHO (1976); more recent information is discussed in section 9.

5.1. General population exposure

5.1.1. Exposure from dental amalgam

5.1.1.1 Human studies

The release of mercury vapour from dental amalgam fillings has been known for a very long time (Stock, 1939). The next major contribution to this field was that

of Frykholm (1957). Using a radioactive mercury tracer, he showed that the insertion of amalgam in both humans and dogs resulted in significant concentrations of mercury in urine and faeces. In humans, the concentration of urinary mercury increased during a 5-day period following the insertion of 4-5 small occlusal fillings. A new higher peak occurred a couple of days after removal of these fillings. Faecal elimination showed a similar pattern, appearing on the second day after amalgam insertion.

Another maximum appeared 1-2 days after amalgam removal. Frykholm (1957) also measured the concentration of mercury in the oral cavity during amalgam placement in teeth. Recently, concern over amalgam usage has been revived by the publication of a number of experimental studies showing that, among other elements, inorganic mercury is released from amalgam *in vitro* (Brune, 1981; Brune & Evje, 1985). More importantly, mercury vapour released in the mouth *in vivo* leads to an increased uptake of mercury in body tissues (Gay et al., 1979; Svare et al., 1981; Abraham et al., 1984; Ott et al., 1984; Patterson et al., 1985; Vimy & Lorscheider, 1985a,b; Vimy et al., 1986; Langworth et al., 1988; Nylander et al., 1987, 1989; Berglund et al., 1988; Aronsson et al., 1989). Vimy & Lorscheider (1985b) showed that the release rate of mercury vapour increases dramatically when the amalgam is stimulated by continuous chewing, reaching a plateau within 10 min. After the cessation of chewing, it takes approximately 90 min for the mercury release rate to decline to the basal pre-chewing value (Fig. 1). A confirmatory study has recently been published by Aronsson et al. (1989), who also made daily dose estimates.

Table 2. Estimated average daily intake and retention (µg/day) of total mercury and mercury compounds in the general population not occupationally exposed to mercury[a]

Exposure	Elemental mercury vapour	Inorganic mercury compounds	Methylmercury
Air	0.030 (0.024)	0.002 (0.001)	0.008 (0.0064)
Food			
Fish	0	0.600 (0.042)	2.4 (2.3)
Non-fish	0	3.6 (0.25)	0
Drinking-water	0	0.050 (0.0035)	0
Dental amalgams	3.8-21 (3-17)	0	0
Total	3.9-21 (3.1-17)	4.3 (0.3)	2.41 (2.31)

[a] From: Environmental Health Criteria 101: Methylmercury (WHO, 1990). 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 2 significant figures.

    Critical reviews have been made of published infor-
mation on mercury release and exposure from amalgam
(Enwonwu, 1987; Friberg & Nylander, 1987; Langan et al.,
1987; Mackert, 1987; Olsson & Bergman, 1987; Clarkson et
al., 1988a). From these reviews it can be concluded that
it is difficult to make accurate quantitative estimations
of the mercury release from amalgam and the uptake of
mercury by the human body. Problems include uncertainty
about analytical quality control, differences in sampling
methodology, breathing pattern, dilution with inhaled air,
and uncertainty about time since previous meals. Due to
these factors, some studies may have overestimated and
others underestimated the daily dose of mercury, while
others may have underestimated or overestimated the mer-
cury uptake.
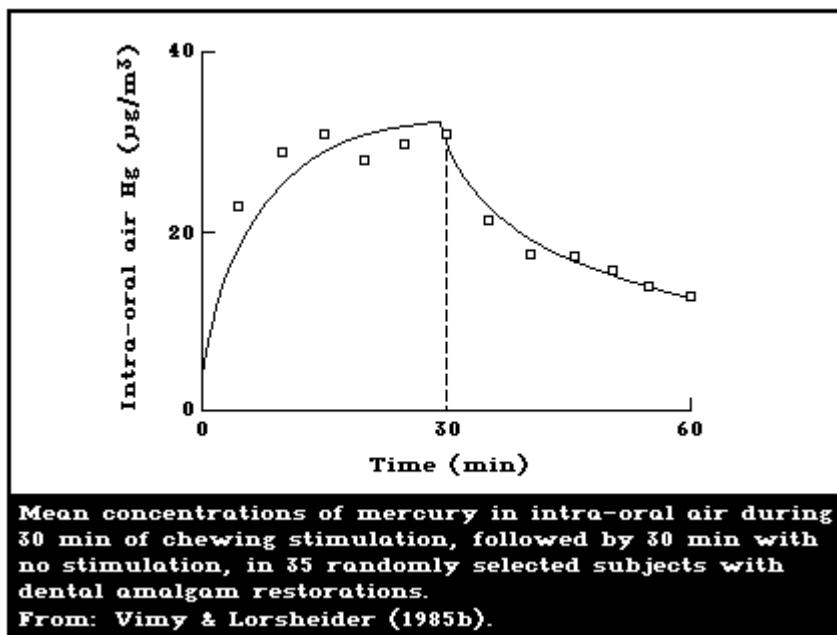
Mean concentrations of mercury in intra-oral air during
30 min of chewing stimulation, followed by 30 min with
no stimulation, in 35 randomly selected subjects with
dental amalgam restorations.
From: Vimy & Lorsheider (1985b).

    Several studies have correlated the number of dental
amalgam fillings or amalgam surfaces with the mercury
content in brain and kidney tissue from human autopsy.
Subjects with no dental amalgam had a mean mercury level
of 6.7 ng/g (2.4-12.2) in the occipital cortex; whereas,
subjects with amalgams had a mean level of 12.3 ng/g
(4.8-28.7) (Friberg & Nylander, 1987; Nylander et al.,
1987). Amalgam-free subjects had a mean mercury level in
kidneys of 49 ng/g (21-105), whereas subjects with amalgam
fillings had a corresponding level of 433 ng/g (48-810).
In a similar investigation, Eggleston & Nylander (1987)
showed mean mercury levels of 6.7 ng/g (1.9-22.1) and 3.8
ng/g (1.4-7.1) in grey and white brain matter, respect-
ively, in subjects with no amalgam fillings. In subjects
with amalgam fillings, mercury levels were 15.2 ng/g
(3.0-121.4) and 11.2 ng/g (1.7-110.1) for grey and white

matter, respectively. In a more recent extensive study,

Schiele (1988) showed a mean brain occipital mercury concentration of 10 ng/g for 44 subjects with an average of 14 amalgam surfaces each. Kidneys from the same subjects showed a sex difference in the mercury concentrations, mean values being 484 ng/g for the 16 females and 263 for the 28 males. Amalgam-free subjects were not included in this study.

Using published experimental data (Svare et al., 1981; Abraham et al., 1984; Patterson et al., 1985; Vimy & Lorsheider, 1985b), the amalgam mercury release rate, average daily mercury uptake, and its steady-state contribution to blood, urine, brain, and kidney were estimated by Clarkson et al. (1988a). These estimations gave brain, kidney, and urine values that are similar to data reported from human studies (brain and kidney autopsy samples: Friberg et al., 1986; Nylander et al., 1987; Schiele, 1988; urine: Nilsson & Nilsson, 1986b; Olstad et al., 1987; Langworth, 1987). A representative illustration of the type of relationship found is given in Fig. 2. Estimates of daily dosages of mercury attributed to amalgam have also been reported by Mackert (1987) and Olsson & Bergman (1987), although they are somewhat lower than those of Clarkson et al. (1988a).

Snapp et al. (1989) studied the blood mercury level before and 18 weeks after the removal of amalgam fillings. After the removal, nine of the ten subjects examined exhibited a statistically significant mean decrease of 1.13 ng (± 0.6) mercury/ml in the blood mercury level.

Recently, Molin et al. (1990) studied mercury concentrations in human plasma, erythrocytes, and urine before and up to 12 months after removal of amalgam fillings and replacements with gold alloy restorations. They noted an initial increase in all recorded mercury levels after amalgam removal. About three months thereafter, plasma and erythrocyte levels decreased markedly. A continuous reduction in urine mercury levels took place, reaching a plateau of approximately 25% of the pre-removal mercury level within 9 months.

It is important to note that, in the studies cited, both the predicted mercury uptake from amalgam and the observed accumulation of mercury in the body are average values. It is also clear from the original reports that substantial individual variations exist.

Relationship between number of amalgam surfaces and urinary mercury concentration. From: Langworth et al. (1988).
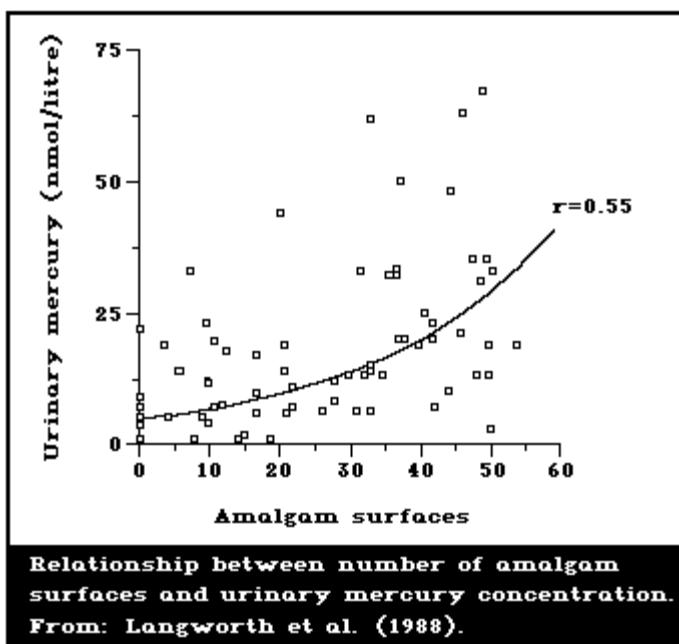
5.1.1.2 Animal experiments

Frykholm (1957), using radioactive mercury in amalgam, studied the release and uptake of mercury in dogs and monkeys. He concluded that the mercury exposure from amalgam was essentially limited to the immediate placement procedures. This is in contrast to more recent studies that examined the disposition of radioactive mercury released from amalgam restorations in sheep (Hahn et al., 1989; Vimy et al., 1990a).

Hahn et al. (1989) demonstrated by whole-body image scan that amalgam mercury could be readily visualized in the kidney, liver, jawbone, and gastrointestinal tract after only 29 days of chewing with amalgam. Vimy et al. (1990a) demonstrated that the mercury levels in maternal blood, fetal blood, and amniotic fluid reached a peak within 48 h after amalgam placement and remained at that level for the duration of the studies (140 days). Mercury levels of 4 ng/g in maternal blood and amniotic fluid and of 10 ng/g in fetal blood were found. The erythrocyte/plasma ratios of mercury from amalgam in both the ewe and fetal lamb were less than unity. The maternal urine mercury concentration ranged from 1-10 ng/g during a 16-day period. Approximately 7.7 mg of mercury could be eliminated per day in the faeces.

All tissues examined displayed mercury accumulation. By 29 days, kidney mercury levels rose to approximately 9000 ng/g, and these levels were maintained throughout the duration of the study. A similar pattern was observed in the liver, but the levels remained at approximately 1000 ng/g. The fetal kidney contained mercury levels of 10-14 ng/g, whereas fetal liver had levels of 100-130 ng/g.

The maternal brain (cerebrum, occipital lobe, and thalamus) showed a mercury accumulation ranging from 3-13 ng/g. In the pituitary, thyroid, and adrenal glands, concentrations ranged from approximately 10-100 ng/g. In the fetal cerebrum, occipital cortex, and thalamus the highest levels were approximately 10 ng/g. The fetal pituitary gland had mercury concentrations of more than 100 ng/g, whereas the thyroid and adrenal glands contained less than 10 ng/g.

Milk obtained at lamb parturition or within several days following birth (25-41 days after amalgam placement) contained levels of mercury from dental amalgam that reached as high as 60 ng/g.

Other recent reports indicate that both kidney function (Vimy et al., 1990b) and intestinal bacterial population (Summers et al., 1990) may be affected when animals are exposed to dental amalgam mercury.

5.1.2. Skin-lightening soaps and creams

Elemental mercury and soluble inorganic mercury compounds can penetrate the human skin. Mercury-containing skin-lightening soaps and creams are left on the skin overnight. Therefore, the possibility of substantial mercury exposure exists both via the skin and through inhalation. There are no empirical data showing the relative importance of the different exposure routes, but the evidence indicates that the total exposure to mercury is substantial from these sources. Barr et al. (1973) reported that in a group of 60 African women using skin-lightening creams (5-10% ammoniated mercury), the mean urinary mercury excretion was 109 µg/litre (range: 0-220 µg per litre). A subgroup of 26 women with a nephrotic syndrome had a mean urinary mercury level of 150 µg/litre (range: 90-250 µg/litre). Marzulli & Brown (1972) reported urinary mercury levels from 28 to 600 µg/litre among a group of 6 women who had used skin-lightening cream containing 1-3% ammoniated mercury for two years.

Lauwerys et al. (1987) reported the case of a woman who had recently given birth and who had used during pregnancy and lactation a soap containing 1% mercury as mercuric iodide and a mercury-containing cream. The urinary mercury content of the mother was 784 µg/g creatinine 4 months after the birth at a time when she was still using the soap and cream. Although no mercury-containing cream or soap was used on her baby's skin and the lactation period lasted only one month, the baby's blood (at the age of three months) contained 19 µg/litre and the urine 274 µg/g creatinine.

5.1.3. Mercury in paint

Mercury compounds are added to water-based latex paints to inhibit the growth of bacteria and mould.

Several reports have highlighted that mercury vapour can be released from the paint on interior house walls (Hirschman et al., 1963; Jacobs & Goldwater, 1965; Foote, 1972; Sibbett et al., 1972).

A recent study by Agocs et al. (in press) compared homes recently coated with a paint containing a median concentration of 754 mg mercury/litre with homes not coated with a mercury-containing paint to determine whether the recent application of such a paint is associated with elevated concentrations of mercury in air and urine. Air samples from the 19 homes of exposed people contained a median level of 2 μg/m^3 (range, undetectable to 10 μg/m^3), while concentrations of mercury in air from 9 homes of unexposed people were below the detection limit of 0.1 μg/m^3 ($p < 0.001$). The median urine mercury concentration was higher for the 65 exposed people (8.4 μg/g creatinine; range, 2.5-118) than for the 28 unexposed people (1.9 μg/g creatinine; range, 0.04-7) ($p < 0.001$).

5.2. Occupational exposure during manufacture, formulation, and use

Occupational exposure to mercury in chloralkali plants and in mercury mining was reviewed in WHO (1976). In more recent studies, average urine mercury levels of 50-100 μg per litre have been reported (see sections 9.1.2 and 9.2.2).

A NIOSH survey in 1983 of 84 workers in a thermometer factory showed that five workers had urinary mercury levels above 150 μg/g creatinine and three workers had levels above 300 μg/g creatinine. Personal air sampling showed exposure levels of 26-271 μg/m^3 (Ehrenberg et al., 1986). Other studies of instrument and thermometer factories in the USA yielded similar results (Price & Wisseman, 1977; Wallingford, 1982; Lee, 1984). In gold and silver refineries in the USA, the mean urinary mercury concentration was 108 μg/litre for four regularly exposed workers (Handke & Pryor, 1981).

Recently, particular interest has focused on occupational exposure to mercury in dentistry (see also section 3.2). Several studies made during the period 1960-1980 have reported average levels of mercury vapour in dental clinics ranging between 20 and 30 μg/m^3 air, and certain clinics have been found to have levels of 150-170 μg/m^3 (Joselow et al., 1968; Gronka et al., 1970; Buchwald, 1972; Schneider, 1974). Some of these studies also reported the urine mercury levels of dental personnel. Joselow et al. (1968) found an average urinary

mercury concentration of 40 μg/litre among 50 dentists, some values exceeding 100 μg/litre. These levels are similar to the urinary mercury concentrations reported by Gronka et al. (1970) and Buchwald (1972).

Kelman (1978) reported statistically significantly higher urine mercury levels among dental assistants (38 µg/litre) than among dentists (22 µg/litre). On the other hand, Nixon et al. (1981) found only small differences between dentists and dental assistants. The average environmental mercury exposure in 200 clinics studied was 11 µg/m^3 (with a range from 0 to 82 µg/m^3), while the mean urine mercury concentration was 26 µg/litre (2-149 µg/litre).

In a nationwide American study by Naleway et al. (1985), the average mercury level in urine sampled between 1975 and 1983 from 4272 dentists was 14.2 µg/litre (SD ± 25.4 µg/litre; the frequency distribution did not resemble a normal distribution), the range being 0-556 µg per litre. In 4.9% of the samples, levels were above 50 µg/litre, and above 100 µg/litre in 1.3% of samples. The wide range of values was probably due to the sampling techniques, methodological problems, and variations in occupational exposures to amalgam.

In a similar Norwegian study, Jokstad (1987) reported that 2% of a group of 672 dentists had urine mercury levels greater than 20 µg/litre. The highest recorded value in this group was 50 µg/litre.

Recently Nilsson & Nilsson (1986a,b) reported a comparatively low mercury level (4 µg/m^3) in the air of private dental clinics. The median urine mercury concentration was 6 µg/litre (range: 1-21 µg/litre) for dentists and 7 µg/litre (range: 1-70 µg/litre) for dental assistants. In a Belgian study of dentists by Huberlant et al. (1983), the mean urine mercury concentration was also relatively low (11.5 µg/g creatinine).

Dentists and dental assistants may be momentarily exposed to high local peaks of mercury vapour during insertion, polishing, and removal of amalgam fillings, especially if adequate protective measures are not taken (Frykholm, 1957; Buchwald, 1972; Cooley & Barkmeier, 1978; Reinhardt et al., 1983; Richards & Warren, 1985). Richards & Warren (1985) reported mercury vapour concentrations approaching 1000 µg/m^3 in the breathing zone of dentists not using coolants or adequate aspiration techniques during operative procedures. The corresponding concentrations when proper measures were used were approximatively ten times lower (110 µg/m^3).

When Battistone et al. (1976) analysed the blood mercury level of 1389 American dentists, the mean value was 9.8 µg/litre (18 dentists having levels above 30 µg per litre). In a study of 380 American dentists, Brady et al. (1980) reported a mean concentration of 8.5 µg per litre, 7.4% of the participants having blood mercury levels greater than 15 µg/litre. These levels were found to decrease within 16 h after termination of exposure.

This finding agrees with the documented short biological half-time in blood for the majority of the mercury (see section 6.5).

These studies suffered from variations in the sampling techniques, the analytical techniques, and the occupational exposure of the participants. Although the extent of occupational exposure could be evaluated from mercury concentrations found in critical organs, few data are available in the literature. Kosta et al. (1975) reported levels of mercury in the central nervous system and the kidneys of deceased mercury miners several years after cessation of exposure. Average levels of 700 µg/kg wet weight of brain (SD ± 640 µg/kg) were, for example, reported in six cases. In the same group plus an additional miner, pituitary mercury levels were reported to be as high as 27 100 µg/kg (SD ± 14 900 µg/kg). Non-exposed controls showed mean brain levels of 4.2 µg per kg (SD ± 2.6 µg/kg, n = 5), mean pituitary levels of 40 µg per kg (SD ± 26 µg/kg, n = 6), and mean kidney levels of 140 µg/kg (SD ± 160 µg/kg, n = 7) (see also sections 9.1.1 and 9.2.1).

A Swedish study of seven former dentists and one dental nurse reported elevated concentrations of mercury in the pituitary gland and occipital lobe cortex (Nylander et al., 1989). Values of up to 4000 µg/kg wet weight were observed in the pituitary gland, and of up to 300 µg/kg in the occipital lobe cortex. Two of the subjects were 80 years old and had been retired for several years. High mercury levels were also noted in the kidneys and thyroid. In one subject, the thyroid concentration was 28 000 µg/kg despite several years retirement.

6. KINETICS AND METABOLISM

There are major differences in the kinetics and metabolism of the various mercury species. Metallic mercury is rapidly oxidized to inorganic mercury compounds in the body. However, its kinetics and membrane permeability are different from those of mercuric mercury. Also methylmercury can be converted to inorganic mercury *in vivo* (WHO, 1990). Thus, the ultimate fate of absorbed mercury compounds will depend on their chemical transformation in the body as well as the kinetics. The details of the kinetics and metabolism of methylmercury have been described in WHO (1990).

6.1. Absorption

6.1.1. Absorption by inhalation

Inhalation of mercury vapour is the most important route of uptake for elemental mercury. Approximately 80% of inhaled mercury vapour is retained. The retention occurs almost entirely in the alveoli, where it is almost 100%. The retained amount is the same whether inhalation

takes place through the nose or the mouth (WHO, 1976; Hursh et al., 1976).

The uptake of metallic mercury vapour from inspired air into the blood depends on the dissolution of mercury vapour in the blood as it passes through the pulmonary circulation. The dissolved vapour is then very soon oxidized to Hg^{++}, partly in the red blood cells and partly after diffusion into other tissues. This oxidation occurs under the influence of the enzyme catalase. The oxidation, and in consequence the absorption, of mercury vapour in humans can be reduced considerably by alcohol or the herbicide aminotriazole (WHO, 1976; Halbach & Clarkson, 1978; Magos et al., 1978; Hursh et al., 1980).

WHO (1976) concluded that information on pulmonary retention of inorganic mercury compounds was lacking. Deposition should follow the physical laws governing deposition of aerosols in the respiratory system. Particulates with a high probability of deposition in the upper respiratory tract should be cleared quickly. For particulates deposited in the lower respiratory tract, a longer retention period would be expected, the length depending on solubility, among other factors. In experiments on dogs, approximately 45% of a radioactive mercury(II) oxide aerosol, with a median droplet diameter of 0.16 (± 0.06) µm, was cleared in less than 24 h and the remainder with a half-time of 33 days (Morrow et al., 1964). Radioactivity was detected in blood as well as in urine. The concentration in blood followed the curve of its disappearance from the lungs. The *in vivo* solubility of the particles was found to be of great importance for the clearance

during the slow phase. Recent evidence has shown that lung macrophages are able to increase the solubility of only slightly soluble metals (Lundborg et al., 1984; Marafante et al., 1987) and that this is due to a low pH in the phagolysosomes (Nilsen et al., 1988).

Although there are still no data to allow a quantitative evaluation of the absorption of different inorganic mercury compounds, significant absorption must take place directly from the lung and, probably, to some extent from the gastrointestinal tract after mucociliary clearance of non-absorbed mercury.

6.1.2. Absorption by ingestion

Liquid metallic mercury is poorly absorbed. Some data indicate an absorption of less than 0.01% in rats. However, humans who accidently ingested several grams of metallic mercury showed increased blood levels of mercury (WHO, 1976). Metallic mercury has been incorporated into tissues after accidental breakage of intestinal tubes, containers, and thermometers. This has sometimes caused local tissue reactions with or without signs of systemic poisoning (Geller, 1976). The reason for the different

types of reactions is not known.

The absorption in humans of inorganic mercuric mercury compounds from foods was estimated by WHO (1976) to be about 7% on average and by Elinder et al. (1988) to be less than 10% (probably about 5%). The data were mainly obtained from tracer studies on human volunteers (Rahola et al., 1973), who received single oral doses of protein-bound inorganic mercuric mercury. Although individual variation was considerable, the proportion of the dose excreted in the faeces during the first 4-5 days was 75-92%.

Absorption in young children may be considerably greater. Kostial et al. (1978, 1983) observed an average absorption in newborn rats of 38% six days after an oral dose of mercuric chloride. The absorption in older animals was only about 1%. As breast milk may contain significant amounts of inorganic as well as organic mercury, this route of exposure should not be overlooked (section 6.4). The low solubility of mercurous chloride limits absorption. However, after prolonged intake the accumulation of mercury in tissues, urinary mercury excretion, and adverse effects indicate that some absorption takes place.

6.1.3. Absorption through skin

Little information was available on skin absorption when WHO (1976) was published, although some animal experiments revealed a certain degree of skin penetration (a few per cent of an aqueous solution of mercuric salts during the first hours of skin application) (Friberg et al., 1961; Skog & Wahlberg, 1964; Wahlberg, 1965). Recent

studies on human volunteers (Hursh et al., 1989) indicate that uptake via the skin of metallic mercury vapour is only about 1% of uptake by inhalation. However, it is obvious that the use of skin-lightening creams containing inorganic mercury salts causes substantial absorption and accumulation into the body (section 5.1.2), although there is no information on how much of the mercury is absorbed through the skin and how much is absorbed via other routes.

6.1.4. Absorption by axonal transport

Arvidson (1987) reported an accumulation of mercury from a tracer dose of $^{203}HgCl_2$ in the hypoglossal nuclei of the brain stem of rats after a single injection into the tongue. A similar accumulation was not seen in controls after a similar injection into the gluteus maximus muscle. The author concluded that the results provided evidence of retrograde axonal transport of mercury in the hypoglossal nerve.

6.2. Distribution

From studies on animals and humans (WHO, 1976; Khayat

& Dencker, 1983a, 1984; see also sections 8 and 9), it is
known that mercury has an affinity for ectodermal and
endodermal epithelial cells and glands. It accumulates in,
for instance, the thyroid, pituitary, brain, kidney,
liver, pancreas, testes, ovaries, and prostate. Within
the organs the distribution is not uniform. This explains
why biological half-times may differ not only between
organs but also within an organ. The kidney is the chief
depository of mercury after the administration of elemen-
tal mercury vapour or inorganic salts. Based on animal
data, 50-90% of the body burden is found in the kidneys.
Significant amounts were transported to the brain after
exposure of mice and monkeys to elemental mercury vapour.
The brain mercury levels were ten times higher than after
equal doses of mercuric mercury given intravenously
(Berlin & Johansson, 1964; Berlin et al., 1969; WHO,
1976). In rats given daily subcutaneous doses of mercuric
chloride for six weeks, only 0.01% of the total dose of
mercury was found in the brain, while about 3% of the dose
was retained in the kidneys (Friberg, 1956).

The red cell to plasma ratio in humans was approxi-
mately 1.0 after exposure to Hg^0 vapour, but was 0.4
after exposure to inorganic mercury salts (WHO, 1976). The
ratio may vary, however. Suzuki et al. (1976) observed a
red cell to plasma ratio of about 1.5-2 for workers
exposed only to mercury vapour, while the corresponding
ratio for 6 chloralkali workers (where the exposure may
have been to both vapour and inorganic salts) averaged
only 0.02. The reason for this extremely low ratio is

unknown. In a report by Cherian et al. (1978), a ratio of
about 2 was observed during the first few days after
exposure of volunteers to metallic mercury vapour.

Jugo (1976) compared the retention of mercuric chlor-
ide after a single injection in adult and 2-week-old suck-
ling rats. The whole-body retention 6 days after treatment
was significantly higher in the suckling animals, and the
accumulation of mercury was 13- and 19-fold higher in the
brain and liver, respectively, compared to adult rats. On
the other hand, the mercury concentrations in the kidneys
were markedly higher in the adult group.

In two pregnant women who had been accidentally
exposed to metallic mercury vapour, the concentration of
mercury in the infant blood was similar to that in the
maternal blood at the time of delivery (Clarkson &
Kilpper, 1978). There are no other data on the transfer of
inhaled mercury vapour to the fetus in humans.

Based on studies in rodents, elemental mercury vapour
easily penetrates the placental barrier and, after oxi-
dation, accumulates in the fetal tissue. Only a fraction
of divalent mercury enters the fetus, but it can accumu-
late in the placenta. Clarkson et al. (1972) found that
mercury levels in the fetuses of rats exposed to mercury

vapour were 10-40 times higher than in animals exposed to equivalent doses of mercuric chloride. Differences in the penetration of the placental barrier have been confirmed in mice by Khayat & Dencker (1982), who found a 4-fold higher fetal mercury concentration after exposure to metallic mercury vapour than after exposure to mercuric chloride. The uptake of mercury vapour increased with gestational age. Only traces of radioactive mercury were found in embryos at 8 and 10 days of gestation. A distinct accumulation of mercury was seen in the fetal tissue from day 12 of gestation with a pronounced uptake in the fetal liver and heart. The mercury concentration in the CNS was rather low in early and mid gestation but increased just prior to birth (Ogata & Meguro, 1986).

Yoshida et al. (1986, 1987) studied the uptake and distribution of mercury in the fetus of guinea-pigs during late gestation after repeated exposure to 200-300 μg mercury vapour/m^3 2 h/day and after a single exposure for 150 min to 8-11 mg/m^3. Mercury concentrations in fetal brain, lungs, heart, kidneys, and blood were much lower than those in maternal tissues, the concentrations differing by a factor of about 5 in the brain and a factor of up to 100 in the kidneys. Mercury concentrations in fetal liver were up to two times higher than those found in maternal liver. In the fetal liver, more than 50% of the mercury was bound to a metallothionein-like protein with a relative molecular mass of about 10 000 to 12 000. The bulk of the eluted mercury in the maternal liver was associated with a protein of high relative molecular mass.

The authors suggested that the fetal metallothionein-like protein plays a role in preventing further distribution of mercury from the liver after *in utero* exposure to mercury vapour.

Mercury distribution in the neonate differs from that in the fetus (Yoshida et al., 1989). A significantly increased level was found in kidney, lung, and brain in neonate guinea-pigs, compared with fetuses, and there was a progressive decrease in liver concentration, with diminishing hepatic metallothionein levels, in the neonates. These results suggest a redistribution of mercury to other tissues in the neonate.

The oxidation of elemental mercury vapour in the body (section 6.1.1) can be reduced considerably (to about 50% of normal values) by moderate amounts of alcohol. In an *in vivo* study, the uptake of labelled mercury into human red cells was reduced by almost a factor of ten by ethanol, while there was an increase in liver mercury concentrations (Hursh et al., 1980). Observations on rats, mice, and monkeys confirm these results (Khayat & Dencker, 1983a,b, 1984). They also show a marked decrease in mercury concentrations in several organs, including the brain. However, somewhat higher concentrations of mercury were observed in the brain and liver of pregnant mice with

a congenital catalase deficiency that were exposed for 1 h
to metallic mercury vapour during day 18 of gestation
(Ogata & Meguro, 1986). The blood mercury concentration
in the catalase-deficient mice was only about half of that
in the control mice. The uptake in the fetus was 2% of the
dose compared to 1.2% for the controls.

Lower mercury levels have been observed in the brain
tissue of humans classified as chronic alcohol abusers
than in controls (Fig. 3).

6.3. Metabolic transformation

Several forms of metabolic transformation occur:

*   oxidation of metallic mercury vapour to divalent mer-
    cury;

*   reduction of divalent mercury to metallic mercury;

*   methylation of inorganic mercury;

*   conversion of methylmercury to divalent inorganic mer-
    cury.

The oxidation of metallic mercury vapour to divalent
ionic mercury (section 6.1.1) takes place very soon after
absorption, but some elemental mercury remains dissolved
in the blood long enough (a few minutes) for it to be
carried to the blood-brain barrier and the placenta (WHO,
1976). Recent *in vitro* studies on the oxidation of mercury
by the blood (Hursh et al., 1988) indicate that because of
the short transit time from the lung to the brain almost

all the mercury vapour (97%) arrives at the brain unoxi-
dized. Its lipid solubility and high diffusibility allow
rapid transit across these barriers. Oxidation of the
mercury vapour in brain and fetal tissues converts it to
the ionic form, which is much less likely to cross the
blood-brain and placental barriers. Thus, oxidation in
these tissues serves as a trap to hold the mercury and
leads to accumulation in brain and fetal tissues (WHO,
1976).
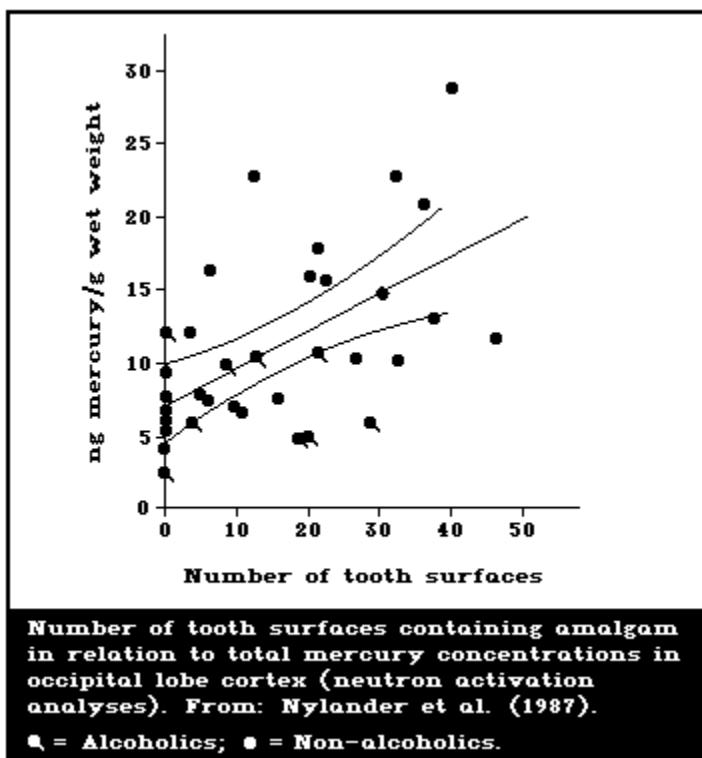
Number of tooth surfaces containing amalgam in relation to total mercury concentrations in occipital lobe cortex (neutron activation analyses). From: Nylander et al. (1987).

◖ = Alcoholics; ● = Non-alcoholics.

The reduction of divalent mercury to Hg^0 has been demonstrated both in animals (mice and rats) and humans (WHO, 1976; Dunn et al., 1978, 1981a,b; Sugata & Clarkson, 1979). A small amount of exhaled mercury vapour is the result of this reduction. It is increased in catalase-deficient mice (Ogata et al., 1987) and by alcohol (both *in vitro* and *in vivo*) in both mice and humans (Dunn et. al., 1981a,b). The increased exhalation of mercury vapour in the latter case may be explained by assuming that the oxidation by catalase is less than normal.

It was stated in WHO (1976) that there is no evidence in the literature for the synthesis of organomercury compounds in human or mammalian tissues. Minor methylation may occur *in vitro* by intestinal or oral bacteria (Rowland et al., 1975; Heintze et al., 1983). A slight increase in the concentration of methylmercury in blood and/or urine has been reported among dentists and workers in the chloralkali industry (Cross et al., 1978; Pan et al.,

1980; Aitio et al., 1983). These data cannot be taken as evidence of methylation, however, due to lack of analytical quality control and possible confounding by exposure to methylmercury. Chang et al. (1987) did not observe any methylation in a study of dentists.

The conversion of methylmercury to inorganic mercury is considered a key step in the process of excretion of mercury after exposure to methylmercury (WHO, 1990). If the intact molecule of an organomercurial in an organ is more rapidly excreted than inorganic mercury, biotrans-

formation will decrease the overall excretion rate, and
the ratio of inorganic to organic mercury in that particu-
lar organ will increase with time. The fraction of total
mercury present as Hg^{++} will depend on the duration of
exposure to methylmercury and/or the time elapsed since
cessation of exposure. Even if the demethylation rate is
very slow, this process may in the long run give rise to
considerable accumulation of inorganic mercury. The ratio
of methylmercury to inorganic mercury depends on the rate
of demethylation and the clearance half-times of methyl-
mercury and inorganic mercury.

After short-term exposure of experimental animals to
methylmercury the kidneys usually contain the highest
fraction of Hg^{++} in relation to total mercury, while the
relative concentration in the brain is low (WHO, 1976).
In studies on squirrel monkeys (Berlin et al., 1975), the
short-term biotransformation to inorganic mercury was as
follows: of the total mercury, about 20% was inorganic in
the liver; 50% in the kidney; 30%-85% in the bile; and
less than 5% in the brain.

More recent data from long-term studies on monkeys
show a different pattern. Mottet & Burbacher (1988) sum-
marized a long series of studies on the metabolism and
toxicity of methylmercury in monkeys *(Macaca fascicu-
laris)*. The monkeys had been orally exposed to high levels
of methylmercury for a period of years and sacrificed
during the ongoing exposure. At the end of the exposure
period, 10-33% of the mercury in the brain was present in
the inorganic form (Lind et al., 1988). In monkeys that
had been without mercury exposure for 6 months to almost
two years after the same treatment, the relative concen-
tration of inorganic mercury was much higher, i.e. about
90%. Exact half-times for the different compounds could
not be established in the absence of data on the concen-
trations of inorganic and organic mercury in the brain at
different time intervals during the accumulation and
clearance phases. Recent data by Rice (1989) also demon-
strate demethylation in the brain. Female monkeys *(Macaca
fascicularis)* were dosed for at least 1.7 years with mer-
cury as methylmercury chloride (10-50 µg/kg per day).
After dosing ceased, the blood mercury half-time was about
14 days. Approximately 230 days after cessation of dosing,

the monkeys were sacrificed and brain total mercury levels
determined. These levels were considered to be at least
three orders of magnitude higher than those predicted by
assuming the half-time in brain to be the same as that in
blood. The author considered the most likely explanation
to be demethylation of methylmercury and subsequent bind-
ing of inorganic mercury to tissue.

Similar results were recently reported by Hansen et
al. (1989) who fed fish contaminated with methylmercury to
one Alsatian dog for 7 years. The dog was examined after
its death at the age of 12 years, 4 years after the

exposure to methylmercury had ceased. Two dogs of the same age and breed served as controls. In the CNS, the mercury was fairly uniformly distributed and 93% was in the inorganic state, whereas the skeletal muscles contained approximately 30% inorganic mercury. The authors concluded that the results demonstrated time-dependent demethylation and suggested a variation in the rate from one type of tissue to another. High levels of mercury were demonstrated by a histochemical method in the liver, thyroid gland, and kidney, whereas practically no mercury was found in any of the organs examined in the control dogs. The distribution of inorganic mercury was determined by a histochemical method for locating mercury in tissue sections. Total mercury was analysed by flameless atomic absorption and organic mercury by GC.

A considerable fraction of the mercury in human brains is reported to be in the form of inorganic mercury. Kitamura et al. (1976) analysed autopsy material from 20 Japanese subjects for total mercury using flameless atomic absorption and for methylmercury using GC. The median concentration of total mercury in the cerebrum was 0.097 mg/kg wet weight and of methylmercury 0.012 mg/kg wet weight. The values for the cerebellum were similar. No analytical quality control data were reported.

In a Swedish autopsy study covering six cases (Friberg et al., 1986; Nylander et al., 1987), about 80% of the mercury in the occipital lobe cortex was inorganic. The concentration of inorganic mercury varied between 3 and 22 µg/kg wet weight. Both total mercury and inorganic mercury were determined by the method of Magos (Magos, 1971; Magos & Clarkson, 1972). For quality control purposes total mercury was also analysed by neutron activation analysis. In this study, however, the concentrations of mercury in the brain were considerably lower than in the Japanese study. As has been discussed in section 5.1.1, an association between the number of amalgam fillings and total mercury concentration in the occipital lobe has been found. Exposure to inorganic mercury from dental fillings could explain the high proportion of inorganic mercury in the Swedish study but not in the Japanese study, as it seems reasonable to assume that the mercury

exposure from amalgam should be approximately the same in the two countries. The exposure to methylmercury could, however, easily differ considerably.

Takizawa (1986) reported the total mercury and methylmercury brain concentrations in about 30 humans who had died from 20 days to 18 years after the onset of symptoms of methylmercury poisoning. The total mercury content was measured by flameless atomic absorption spectrophotometry, while methylmercury was analysed by electron capture GLC (Minagawa et al., 1979; Takizawa, 1986). The total mercury content in "acute" cases (autopsy < 100 days after onset of symptoms) was 8.8-21.4 mg/kg and the concentration of

methylmercury was 1.85-8.42 mg mercury/kg. The concen-
trations for the "chronic" cases were 0.35-5.29 mg/kg
for total mercury and 0.31-1.02 mg mercury/g for methyl-
mercury. On average, only 28% of the mercury was present
as methylmercury in the acute cases and 17% in the chronic
cases. Takizawa (1986) also presented data for residents
near Minamata Bay and for a non-polluted area. The best
estimate from these data is that only 16% and 12%,
respectively, of the total mercury was present as methyl-
mercury. Unfortunately, in these reports quality control
data were not presented. The authors measured total mer-
cury and methylmercury and assumed that the difference
between these analyses was due to inorganic mercury. It
could in principle, in whole or in part, also have been
methylmercury that was not extracted in the gas chromato-
graphic procedure. Ideally, analyses should be carried out
using, for instance, the method by Magos (1971), which
measures total mercury and inorganic mercury.

The tissues in the studies by Takizawa (1986) were
stored for long periods after fixation with a 10% neutral
formalin solution. Miyama & Suzuki (1971) found that the
ratio of inorganic to total mercury in the cerebral cortex
increased from about 35% (tissues stored frozen) to about
50% after storage in 10% formalin for one year. However,
there was no loss of inorganic mercury. Eto et al. (1988)
compared results from a small number of analyses of
formalin-fixed tissues with results from analyses of
frozen tissues. There was no systematic loss related to
storage in formaldehyde.

The concentrations of inorganic mercury in the brain,
reported in overt cases of methylmercury poisoning, are
very high, similar to those observed after toxic exposure
to metallic mercury vapour. Whether or not an accumulation
of inorganic mercury actually contributed to the toxic
effects is not known, but seems unlikely. Even assuming
no analytical problems, it should be borne in mind that
the methylmercury poisoning usually occurred after rela-
tively short exposure to methylmercury when no significant
biotransformation should yet have taken place. However, a
comparison of the toxicology of methylmercury with that of

ethylmercury, which decomposes significantly more quickly,
indicated that cerebellar damage could not be related to
inorganic mercury. The higher concentration of inorganic
mercury in the brain of ethylmercury-treated rats, com-
pared with methylmercury-treated rats, was associated with
less cerebellar damage (Magos et al., 1985). It is more
difficult to evaluate the possible long-term effects of
inorganic mercury, which slowly accumulates in the brain.

The distribution of ionic mercury in the brain will
depend on whether Hg^{++} enters the brain in the ionic form
or as a result of *in situ* biotransformation following
penetration of the brain barrier by elemental mercury or
methylmercury. The toxicological aspects of such possible

differences in distribution are not known.

6.4. Elimination and excretion

A small portion of absorbed inorganic mercury is exhaled as metallic mercury vapour, formed by the reduction of Hg^{++} in the tissues (Dunn et al., 1978), but urine and faeces are the principal routes of elimination (WHO, 1976). The urinary route dominates when exposure is high. After exposure to metallic mercury vapour, a small fraction of the mercury in the urine may be present as elemental mercury (Stopford et al., 1978; Yoshida & Yamamura, 1982). One form of depletion is the transfer of maternal mercury to the fetal unit. Thus, inorganic mercury was detected in the amniotic fluid in all but two out of 57 Japanese pregnant women, while organic mercury was found in only 30 women (Suzuki et al., 1977). In a study by Skerfving (1988), it was reported that the concentrations of total mercury in breast milk and in the blood plasma of breast-fed infants were similar to those in the maternal plasma of Swedish fishermen's wives. Although the women were exposed to methylmercury, 80% of mercury excreted in breast milk was in the inorganic form. No formal analytical quality control procedures were applied in the studies where mercury was speciated.

6.5. Retention and turnover

6.5.1. Biological half-time

Only very limited data were available on the biological half-time of inorganic mercury when WHO (1976) was published. Studies on a small number of volunteers had shown that the elimination of mercury, after a single exposure to metallic mercury vapour, followed a single exponential process with an average half-time of 58 days during the first few months after the exposure. Similar data were available from studies involving oral exposure to mercuric mercury. It was pointed out that there had been a few reports of high brain mercury concentrations in workers several years after cessation of exposure to

mercury vapour. This indicated that the half-time in brain is longer than that in other organs, although no quantitative estimations were made.

As a result of tracer studies on human volunteers (Nakaaki et al., 1975, 1978; Cherian et al., 1978; Newton & Fry, 1978; Hursh et al., 1980) and animals (Berlin et al., 1975), more data are now available on the kinetics during the first few months after exposure. The elimination of inorganic mercury follows a complicated pattern with biological half-times that differ according to the tissue and the time after exposure. The best estimate is that after short-term exposure to mercury vapour, the first phase of elimination from blood has a half-time of approximately 2-4 days and accounts for about 90% of the

mercury.   This is followed by a second phase with a half-time of 15-30 days.

In tracer studies on nine human volunteers (Hursh et al., 1976, 1980; Clarkson et al., 1988a) the half-time for most of the mercury in the brain was 19 (± 1.7) days during the first 35 to 45 days. Newton & Fry (1978) found half-times of 23 and 26 days in the head of two subjects accidentally exposed to radioactive mercuric oxide. In a study by Berlin et al. (1975), a steady state was not reached in the brains of squirrel monkeys exposed for two months to mercury vapour. In one study on monkeys *(Macaca fascicularis)* (section 6.3) lasting several years where inorganic mercury accumulated in the brain (probably as a result of demethylation of methylmercury), there was still considerable inorganic mercury in the brain 1-2 years after cessation of exposure (Lind et al., 1988). These results indicate a very long half-time for a fraction of the inorganic mercury in the brain. This is in accordance with data from deceased miners and dentists (section 5.2).

The half-time in the kidneys for inorganic mercury in the studies by Hursh et al. (1976, 1980) was 64 days, about the same as that for the body as a whole. As in the case of the brain, a fraction of the mercury probably has a long biological half-time (section 5.2).

A few attempts to perform a quantitative evaluation of the half-time for inorganic mercury have been made using multicompartment models (Sugita, 1978; Bernard & Purdue, 1984). According to the recommendation of ICRP (1980), the four-compartment model of Bernard & Purdue (1984) included one compartment with a half-time of 27 years. As the basic assumptions are uncertain, the models are uncertain, but may be of value for a possible "worst case" estimation of the retention of inorganic mercury in the brain.   The model of Bernard & Purdue (1984) has been used by Vimy et al. (1986) for calculating mercury accumulation in the

brain from amalgam fillings (section 5.1). The form of mercury that is responsible for the long biological half-time may be biochemically inactive mercury selenide.

6.5.2. Reference or normal values in indicator media

A considerable amount of information is given in Environmental Health Criteria 101: Methylmercury (WHO, 1990). The mean concentration of total mercury in whole blood (in the absence of consumption of fish with high concentrations of methylmercury) is probably of the order of 5-10 µg/litre,   and in hair about 1-2 mg/kg. The aver-age mercury concentration in urine is about 4 µg   per litre and in the placenta about 10 mg/kg wet weight, although the individual variation is substantial. One source of the variation in urine levels seems to be exposure from dental amalgam (Fig. 4), while for blood and

hair levels fish consumption is the major source of ex-
posure. Increased hair levels may also be due to external
contamination.

Creatinine-adjusted urinary mercury values
(Hg/CR) in relation to amount of amalgam
restoration (amalgam points). Broken line:
linear regression line (r = 0.55).
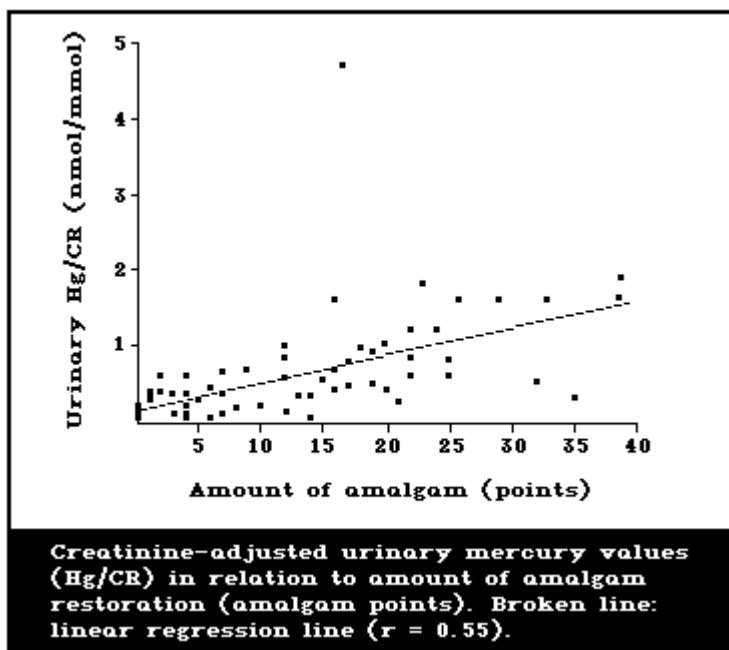
There are at present no suitable indicator media that
will reflect concentrations of inorganic mercury in the
critical organs, the brain or kidney, under different
exposure situations. This is to be expected in view of the
complicated pattern of metabolism for different mercury
compounds. One important consequence is that concen-
trations of mercury in urine or blood may be low quite
soon after exposure has ceased, despite the fact that
concentrations in the critical organs may still be high.

There is some information, obtained from subjects not
occupationally exposed and with only a moderate fish
consumption, on the relationship between exposure to
metallic mercury vapour and concentrations of mercury in
urine and brain tissue. This relationship (section 5.1)
indicates that ongoing long-term exposure to elemental
mercury vapour, leading to a mercury absorption of
5-10 µg/day, will result in a mercury excretion in urine
of about 5 µg/litre and average mercury concentrations
in the occipital lobe cortex and kidney of approximately
10 µg/kg and 500 µg/kg, respectively.

The distribution between blood and hair is well known
for different exposure levels of methylmercury, which
forms the basis for the use of hair as an indicator media
for this compound. There is no corresponding information
for inorganic mercury. When high levels of total mercury
in hair have been reported, for instance, among dentists
exposed to metallic mercury vapour (see e.g. Sinclair et
al., 1980; Pritchard et al., 1982; Sikorski et al., 1987),

it was not known how much was due to external contamination. In a report on biological monitoring of toxic metals, Elinder et al. (1988) concluded that hair is not a suitable indicator medium for monitoring exposure to inorganic mercury.

There is good epidemiological evidence from occupational exposure that, on a group basis, recent exposure is reflected in the mercury levels in blood and urine. When exposure is low (e.g., from amalgam), it is difficult to find an association between exposure levels and blood concentrations due to confounding exposures to methylmercury in fish. A way to overcome the problem may be to analyse mercury in plasma or speciate the analysis for inorganic mercury (Elinder et al., 1988). The problem of confounding exposures is not so important when analysing urine, as only a very small fraction of absorbed methylmercury is excreted in urine.

Data amassed by Smith et al. (1970) from the chlorine industry were used by WHO (1976) to evaluate the relationship between concentrations of metallic mercury vapour in air and concentrations of mercury in blood and urine. Long-term time-weighted occupational exposure to an average air mercury concentration of 50 µg/m^3 was considered to be associated, on a group basis, with blood mercury levels of approximately 35 µg/litre, and with urinary concentrations of 150 µg/litre. The ratio of urine to air concentrations was re-evaluated by WHO (1980) to be closer to 2.0-2.5 instead of 3.0. The mercury concentrations in air were measured with static samplers. Results from a number of more recent studies have been reported where both static samplers and personal samplers have been used (Ishihara et al., 1977; Lindstedt et al., 1979; Müller et al., 1980; Mattiussi et al., 1982; Roels et al., 1987).

Where personal samplers have been used, the ratio between urinary mercury (µg/litre or per g creatinine) and mercury in air (µg/m^3) has as a rule been 1-2. When blood values were reported they were either similar to those given in WHO (1976) or somewhat lower.

In the study by Roels et al. (1987), personal monitoring was used, detailed quality control procedures were implemented and reported, and the examined subjects had been exposed to defined concentrations for at least one year. A good relationship could be established between the daily time-weighted exposure to mercury vapour and the daily level of mercury in blood and urine (Fig. 5A and B). Urinary levels of about 50 µg/g creatinine were seen after occupational exposure to about 40 µg/m^3 of air. Such an exposure would correspond to about 17 µg/litre of blood.

Several studies have reported a correlation between mercury in blood and urine. The results vary considerably and it is not known whether the ratio between concentrations in urine and blood is constant at different

exposure levels. At low exposure levels the possibilities
of a significant confounding effect on blood levels should
always be borne in mind.

Relationships between individual daily levels
of mercury in air on hopcalite filters by
personal sampler and those in blood samples
taken at the end of the work shift (14.00 h).
From: Roels et al. (1987).

Relationships between individual daily levels
of mercury in air on hopcalite filters by
personal sampler and those in urine samples
collected the following morning (9.00 h).
From: Roels et al. (1987).

On the basis of studies by Smith et al. (1970) and
Lindstedt et al. (1979), Skerfving & Berlin (1985)
suggested that a urine mercury level of 50 µg/g creati-
nine is associated with a blood mercury level of 20 µg

per litre. Roels et al. (1987) reported a regression equation, where a urine mercury level of 50 µg/g creatinine leads to a blood mercury level of 16 µg/litre.

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

This chapter is extracted from the summary of Environmental Health Criteria 86: Mercury - Environmental Aspects (WHO, 1989).

7.1. Uptake, elimination, and accumulation in organisms

Mercuric salts, and, to a much greater extent, organic mercury, are readily taken up by organisms in water. Aquatic invertebrates, and most particularly aquatic insects, accumulate mercury to high concentrations. Fish also take up the metal and retain it in tissues, principally as methylmercury, although most of the environmental mercury to which they are exposed is inorganic. The source of the methylation is uncertain, but there is strong indication that bacterial action leads to methylation in aquatic systems. Environmental levels of methylmercury depend upon the balance between bacterial methylation and demethylation. The indications are that methylmercury in fish arises from this bacterial methylation of inorganic mercury, either in the environment or in bacteria associated with fish gills, surface, or gut. There is little indication that fish themselves either methylate or demethylate mercury. Elimination of methylmercury is slow from fish (with half times in the order of months or years) and from other aquatic organisms. Loss of inorganic mercury is more rapid and so most of the mercury in fish is retained in the form of methylmercury. Terrestrial organisms are also contaminated by mercury, with birds being the best studied. Sea birds and those feeding in estuaries are most contaminated. The form of retained mercury in birds is more variable and depends on species, organ, and geographical site.

7.2. Toxicity to microorganisms

The metal is toxic to microorganisms. Inorganic mercury has been reported to have effects at concentrations of the metal in the culture medium of 5 µg/litre, and organomercury compounds at concentrations at least 10 times lower than this. Organomercury compounds have been used as fungicides. One factor affecting the toxicity of the organometal is the rate of uptake of the metal by cells. Mercury is bound to the cell walls or cell membranes of microorganisms, apparently to a limited number of binding sites. This means that effects are related to cell density as well as to the concentration of mercury in the substrate. These effects are often irreversible, and mercury at low concentrations represents a major hazard to microorganisms.

7.3. Toxicity to aquatic organisms

The organic forms of mercury are generally more toxic
to aquatic organisms than the inorganic forms. Aquatic
plants are affected by mercury in the water at concen-
trations approaching 1 mg/litre for inorganic mercury but
at much lower concentrations of organic mercury. Aquatic
invertebrates vary greatly in their susceptibility to
mercury. Generally, larval stages are more sensitive than
adults. The 96-h LC_{50}s vary between 33 and 400 µg per
litre for freshwater fish and are higher for sea-water
fish. However, organic mercury compounds are more toxic.
Toxicity is affected by temperature, salinity, dissolved
oxygen, and water hardness. A wide variety of physiologi-
cal and biochemical abnormalities has been reported after
fish have been exposed to sublethal concentrations of
mercury, although the environmental significance of these
effects is difficult to assess. Reproduction is also
affected adversely by mercury.

7.4. Toxicity to terrestrial organisms

Plants are generally insensitive to the toxic effects
of mercury compounds. Birds fed inorganic mercury show a
reduction in food intake and consequent poor growth.
Other, more subtle, effects on enzyme systems, cardio-
vascular function, blood parameters, the immune response,
kidney function and structure, and behaviour have been
reported. Organomercury compounds are more toxic for birds
than are inorganic.

7.5. Effects of mercury in the field

Pollution of the sea with organomercury led to the
death of fish and fish-eating birds in Japan. Except for
this incident at Minamata, few follow-up studies of the
effects of localized release have been conducted. The use
of organomercury fungicides as seed dressings in Europe
led to the deaths of large numbers of granivorous birds,
together with birds of prey feeding on the corpses. Resi-
dues of mercury in birds' eggs have been associated with
deaths of embryos in shell. The presence of organochlorine
residues in the same birds and their eggs makes an accu-
rate assessment of the effects of mercury difficult. It
is, however, thought to be a contributing factor in the
population decline of some species of raptors.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1. Single and short-term exposure

Ashe et al. (1953) reported evidence of damage to
brain, kidney, heart, and lungs in rabbits exposed acutely
to metallic mercury vapour at a mercury concentration of
29 mg/m^3 of air.

The LD_{50} for inorganic mercury, as well as for a num-
ber of organomercurials (e.g., arylmercury, alkoxyalkyl-

and alkylmercury compounds), lies between 10 and 40 mg/kg body weight for all compounds tested. For mercuric chloride, a value of about 10 mg/kg body weight has been observed after parenteral administration to mice. The similarity in LD_{50} values for these various types of mercury compounds is considered to result from the fact that, when given in acute massive doses, mercury in any chemical form will denature proteins, inactivate enzymes, and cause severe disruption of any tissue with which it comes into contact in sufficient concentrations. The features of acute toxicity usually consist of shock, cardiovascular collapse, acute renal failure, and severe gastrointestinal damage.

8.2. Long-term exposure

8.2.1. General effects

WHO (1976), in evaluating a number of experimental studies on animals, concluded that both reversible and irreversible toxic effects may be caused by mercury and its compounds. Microscopically detectable changes have been seen in the organs of dogs, rabbits, and rats exposed to concentrations of elemental mercury vapour ranging from about 100 to 30 000 $\mu g/m^3$ for different periods of time. Severe damage was noted in kidneys and brains at mercury levels in air of about 900 $\mu g/m^3$ after an exposure period of about 12 weeks. After exposure of dogs to 100 μg mercury/m^3, for 7 h/day, 5 days/week over a period of 83 weeks, no microscopically detectable effects were seen, and tests revealed no abnormalities in kidney function.

In two studies (Fukuda, 1971; Kishi et al., 1978), tremor and behavioural effects were observed in rabbits and rats after several weeks of exposure to metallic mercury vapour at levels of several mg/m^3, although there were no morphological changes in the brain. The symptoms were associated with brain mercury concentrations of about 1 and 20 mg/kg wet weight in the two studies.

8.2.2. Immunological effects

During the last 10-20 years, great attention has been paid to effects of inorganic mercury on the immune system. An important conclusion is that, depending upon the animal strain tested, either auto-immunity or immunosuppression is observed.

8.2.2.1 Auto-immunity

Bariety et al. (1971) showed that about 30% of outbred Wistar rats exposed to mercuric chloride (1.5 or 2.5 mg/kg body weight) 3 times per week for periods of several months developed a membranous glomerulopathy characterized by granular, subepithelial deposits of IgG and C_3.

In Brown Norway rats (Sapin et al., 1977; Druet et al., 1978) and in New Zealand rabbits (Roman-Franco et al., 1978) injected with 1 or 2 mg/kg body weight, a systemic auto-immune disease was observed. It appeared in 100% of the rats tested. This disease is characterized by the production of auto-antibodies to renal and extra-renal basement membranes. These antibodies are specific for laminin, type IV collagen, and entactin (Bellon et al., 1982; Fukatsu et al., 1987) and are found deposited along the glomerular basement membrane in a linear pattern. After 3 to 4 weeks, a typical membranous glomerulopathy with granular, subepithelial IgG deposits is observed. The majority of rats develop proteinuria, which progresses in some animals to the nephrotic syndrome (Druet et al., 1978). About half of those with this syndrome die. However, the remainder recover since the disease is transient. Dermatitis and Sjogren's syndrome have been recently detected in Brown Norway rats injected with mercuric chloride (Aten et al., 1988). Contact sensitization to mercury has also been reported to occur in susceptible strains of guinea-pigs (Polak et al., 1968). Auto-immunity in Brown Norway rats appears in the context of a polyclonal activation of B cells. There is a lymphoproliferation (increase in the number of CD4+ T cells and B cells) and hyperimmunoglobulinaemia affecting mainly IgE (Prouvost-Danon et al., 1981; Hirsch et al., 1982; Pelletier et al., 1988a), and several auto-antibodies such as antinuclear antibodies (Hirsch et al., 1982) are produced. All these manifestations are transient. They appear from day 8 following the injection, peak during the third week, and then progressively decline.

A number of other studies have been carried out using Brown Norway rats. Low doses of mercuric chloride (50 µg/kg body weight given 3 times per week) induced auto-immune glomerulopathy, while 100 µg/kg body weight (also 3 times per week) induced both auto-immune glomerulopathy and proteinuria. Mercuric chloride was also effective when given by inhalation (aerosol or intratracheal instillation) or ingestion (Bernaudin et al., 1981;

Andres, 1984; Knoflach et al., 1986). Other inorganic mercury compounds, e.g., mercurous chloride given orally or $HgNH_2Cl$-containing ointments, also induce auto-immunity (Druet et al., 1981).

Auto-immune disorders including auto-immune glomerulopathy have been described in other strains of rats (Weening et al., 1978; Druet et al., 1982). In susceptible strains of mice, especially those mice carrying the $H-2^s$ haplotype, long-term exposure to mercuric chloride induces extremely high titres of antinucleolar auto-antibodies (Robinson et al., 1986; Mirtscheva et al., 1987). These auto-antibodies and circulating immune complexes (Hultman & Eneström, 1987) are involved in the glomerular IgG deposits found in the mesangium and in the vessel walls of $H-2^s$ mice treated with mercuric chloride

(Hultman & Eneström, 1988). Analysis of the fine specificity of the antinucleolar auto-antibodies revealed that at least some of them react with fibrillarin, a component of U3 small nuclear ribonucleoprotein. Sera from human patients with idiopathic scleroderma contain auto-antibodies with exactly the same specificity (Reuter et al., 1989).

8.2.2.2 Genetics

Rats with certain major histocompatibility haplotypes, such as Lewis rats, are resistant whatever the dose used, while other strains are susceptible (Table 3). The susceptibility of segregants obtained by crossing Brown Norway and Lewis rats has been extensively studied (Druet et al., 1977, 1982; Sapin et al., 1984). It has been demonstrated that susceptibility depends upon 3 or 4 genes. One of them is located within the major histocompatibility complex. Both the major histocompatibility complex-linked and -unlinked genes are required for these auto-immune abnormalities to occur.

Table 3. Susceptibility of various strains of rats to auto-immune glomerulonephritis induced by mercuric chloride

Strain	RT-1 haplotype[a]	Auto-immune glomerulonephritis
BN	n	anti-GBM[b]; MGP[c]
LEW, F/344	l	none
BS, AS, BD IX	l	none
BN-1L[d]	l	none
LEW-1N[d]	n	none
PVG/c, AUG	c	glomerular granular deposits
DA, AVN	a	glomerular granular deposits
AS$_2$	f	glomerular granular deposits
OKA	k	glomerular granular deposits

Table 3 (contd.)

BUF	b	glomerular granular deposits
BD V	d	glomerular granular deposits
WAG, LOU	u	none
Wistar Furth	u	MGP

[a] Major histocompatibility complex in the rat.
[b] Antiglomerular basement membrane antibodies.
[c] Membranous glomerulopathy.
[d] Congenic rats with the l RT-1 haplotype on the BN background (BN-1L) or with the n haplotype on the LEW background (LEW-1N).

8.2.2.3 Mechanisms of induction

Mechanisms of induction have been thoroughly studied in rats. Mercuric chloride induces in Brown Norway rats a

polyclonal activation of B cells (Hirsch et al., 1982; Pelletier et al., 1988a). T cells are required, since Brown Norway rats with the nude mutation or depleted of T cells are resistant (Pelletier et al., 1987a). It appears that mercuric chloride induces in this rat strain the appearance of T cells able to stimulate class II determinants (also called Ia antigens), which are expressed on the cell membrane of all B cells (Pelletier et al., 1986). The role of such T cells is strongly supported by the fact that T cells from Brown Norway rats injected with mercuric chloride are able to transfer auto-immune manifestations to normal Brown Norway recipients and also to Brown Norway rats depleted of T cells (Pelletier et al., 1988b). This strongly suggests that T cells from rats injected with mercuric chloride are able to stimulate B cells directly. The autoreactive, anticlass II, T cells which recognize normal B cells as well as B cells from rats injected with mercuric chloride may have initially been induced following a modification of class II determinants by mercury, as suggested by Gleichmann et al. (1984). It is also possible that mercuric chloride affects CD8+ (suppressor/cytotoxic) T cells, as suggested by Weening et al. (1981).

The fine mechanism of action at the cellular level (see section 8.7) remains to be elucidated.

8.2.2.4 Autoregulation

The auto-immune disease observed in Brown Norway rats is self-regulated. Abnormalities progressively disappear after the third week. It has been shown that CD8+ (suppressor/cytotoxic) T cells are responsible for this effect (Bowman et al., 1984), together with the appearance of auto-anti-idiotypic antibodies (Chalopin & Lockwood, 1984).

8.2.2.5 Immunosuppression

Lewis rats do not develop auto-immune disorders when injected with mercuric chloride. In contrast, CD8+ (suppressor/cytotoxic) T cells proliferate in the spleen and in the lymph nodes of such animals. As a consequence they develop a non-antigen-specific immunosuppression (Pelletier et al., 1987c). They do not respond either to classical mitogens or to allo-antigens. More interestingly, mercuric chloride is able to inhibit the development of organ-specific auto-immune disorders such as Heymann's nephritis (Pelletier et al., 1987b) and experimental allergic encephalomyelitis (Pelletier et al., 1988c). The mechanisms are not yet understood.

The mercury model represents a unique tool for evaluating the relationship between genetic and chemically induced immune disregulation.

8.2.2.6 Conclusions

It may be concluded that the most sensitive adverse effect caused by mercuric mercury is the formation of mercuric-mercury-induced auto-immune glomerulonephritis, the first step being the production and deposition of IgG antibodies to the glomerular basement membrane. The Brown Norway rat is a good test species for the study of mercuric-mercury-induced auto-immune glomerulonephritis, although this effect has also been observed in rabbits. Table 4 presents the available studies on auto-immune glomerulonephritis. The lowest-observed-adverse-effect level found in these studies was 16 mg/kg per day via the subcutaneous route of exposure.

8.3. Reproduction, embryotoxicity, and teratogenicity

8.3.1. Males

Very little information on male reproductive effects is available. Lee & Dixon (1975) injected male mice with single doses of mercuric chloride (1 mg mercury/kg body weight) and found a significant decrease in fertility, compared with controls, in controlled mating tests. Normal fertility was restored after about 2 months. In studies by Chowdhury et al. (1986), gradual alterations in testicular tissues were noted in rats treated with mercuric chloride at intraperitoneal dosages of 0.05 mg/kg and 0.1 mg/kg body weight over a period of 90 days. There was a decrease in seminiferous tubular diameter, spermatogenic cell counts, and Leydig cell nuclear diameter, compared with controls.

Table 4. Auto-immune effects of mercuric mercury on the glomerular basement membrane

Animal	Route	Duration	Adverse effect level (mg/kg per day)	Reference
Brown Norway rat	oral	60 days	320	Bernaudin et al. (1981)
Brown Norway rat	oral	60 days	630	Andres (1984)
Brown Norway rat	subcutaneous	12 weeks	16	Druet et al. (1977)
Brown Norway rat	subcutaneous	8 weeks	32[a]	Druet et al. (1978)
Rabbit	intramuscular	1–17 weeks	633	Roman-Franco et al. (1978)

[a] Proteinuria was observed, in addition to the auto-immune glomerulonephritis, in these rats.

8.3.2. Females

Lamperti & Printz (1973) injected female hamsters with daily doses of 1 mg mercuric chloride (8-11 mg mercury/kg) throughout one 4-day estrous cycle (the LD_{50} being 18 mg mercury/kg body weight). There were effects on the reproductive system, including morphological changes of corpora lutea and inhibition of follicular maturation. In further studies (Lamperti & Printz, 1974), it was reported that 60% of female hamsters did not ovulate by day one of the third estrous cycle after having been given a total of 3-4 mg mercuric chloride during the first estrous cycle. Watanabe et al. (1982) injected female hamsters with mercuric chloride at high doses (6.4 or 12.8 mg mercury/kg body weight) during day one of the estrous cycle and observed an inhibition of ovulation. Lamperti & Niewenhuis (1976) injected female hamsters with 1 mg mercuric chloride per day during one estrous cycle and found significantly higher levels of follicle-stimulating hormone in the pituitary gland, compared with controls.

Several investigators have reported abortions following exposure to elemental mercury vapour or inorganic mercury compounds several days after implantation. There are also reports of decreased fetal weight and malformations. Gale & Ferm (1971) injected three groups of female hamsters with a single dose of 2, 3, or 4 mg mercuric acetate (about 1.3-2.5 mg mercury) intravenously on day 8 of gestation. The exposed groups showed resorption

frequencies of 12, 34, and 52%, respectively, compared to 4% in the controls. The mothers showed signs of mercury intoxication in the form of weight loss, kidney lesions, and diarrhoea. In later studies (Gale, 1980, 1981), a single injection of mercuric acetate (15 mg/kg body weight) to hamsters produced a cluster of cardiac and non-cardiac abnormalities. The most important aspects of embryotoxicity were resorptions, retardation, and abnormal heart. Significant but varied interstrain differences were observed. Holt & Webb (1986) exposed pregnant Wistar rats intravenously to mercuric chloride at different periods of gestation. During mid-gestation the minimum effective teratogenic dose of mercury (0.79 mg/kg total body weight) was high in relation to the maternal LD_{50} and the incidence of fetal malformations, mainly brain defects, was 23% in all live fetuses. In rats of different gestational ages, uptake of Hg^{2+} by the fetus at this dose level decreased sharply between day 12 and day 13. The teratogenic effects on the fetus and damage to the maternal kidneys, however, were essentially the same in animals dosed with Hg^{2+} either immediately before or immediately after these gestational ages. The authors considered it probable, therefore, that fetal defects resulted not from any direct action of Hg2+ on the conceptuses but either from the inhibition of the transport of essential metabolites from the mother or from maternal kidney dysfunc-

tion.

In a study by Rizzo & Furst (1972), three groups of female rats were exposed to single oral doses of mercuric oxide equivalent to 2 mg mercury/dose. Each dose of mercury was given suspended in 2 ml peanut oil. The three groups received the mercury on day 5, 12, or 19 after conception. External malformations were observed in 29.7%, 6.8%, and 3.4% of cases, respectively, while the three control groups had values between 0 and 2%. The two observable effects that mercury had on rat fetuses were arrest of general growth, as indicated by the number of runts, and inhibition of eye formation. The mothers showed no effects from the treatment. The data, if confirmed, are of particular interest, as mercuric oxide is fairly insoluble.

Steffek et al. (1987) reported the effects of elemental mercury vapour exposure on pregnant Sprague-Dawley rats. The rats were exposed to elemental mercury vapour at concentrations of 100, 500, or 1000 $\mu g/m^3$ during the entire gestational period (chronic exposure) or during the period of organogenesis (days 10-15, acute exposure). Macroscopic examination of fetuses obtained from pregnant rats exposed acutely or chronically to 100 $\mu g/m^3$ revealed no increased incidence of congenital malformations or resorptions when compared to room or chamber controls. However, acute exposure to 500 $\mu g/m^3$ resulted in an increase in the number of resorptions (5/41), and chronic

exposure at this concentration resulted in two fetuses (out of 84 that were examined) with cranial defects. There were also single cases of encephalomeningocoele, dome-shaped cranial configuration, and cleft palate (Steffek, A.J., written personal communication to the American Dental Association). Acute exposure at 1000 $\mu g/m^3$ resulted in an increase in the rate of resorptions (8/71), and chronic exposure at this dose level produced a decrease in maternal and fetal weights, relative to the control groups, and an increase in the number of resorptions (7/28).

8.4. Mutagenicity and related end-points

Mercuric mercury affects the mitotic spindle in plants, which may lead to an abnormal distribution of chromosomes (Ramel, 1972; Leonard et al., 1983). It is not a potent inducer of dominant lethal mutations in mice (Suter, 1975). Zasukhina et al. (1983) reported the induction of single-stranded DNA breaks after exposure of cultures of mice embryo cells to mercury chloride. The mercury did not induce mutations but had a strong lethal effect in a survival test of vaccinia virus. A shortening of the chromosome length in human lymphocytes exposed *in vitro* has been observed (Andersen et al., 1983). Mercuric mercury did not induce chromosomal aberrations in human lymphocytes and in mammalian cells *in vitro* (Paton &

Allison 1972; Umeda & Nishimura, 1979). Positive results in the recombination assay with mercuric chloride have been reported by Kanematsu et al. (1980). Effects have been reported on DNA repair in mammalian cells (Robison et al., 1984). There was an increase in C-mitotic figures and segregational errors in human lymphocytes and in Indian muntjac fibroblasts (Verschaeve et al., 1984, 1985). Based on studies of *Drosophila melanogaster,* Magnusson & Ramel (1986) found a pronounced variation in tolerance between 12 wild type strains when testing a number of metal compounds, including mercuric chloride. Morimoto et al. (1982) reported that in human whole blood cultures selenite prevents the induction of sister-chromatid exchanges by mercuric chloride.

The US Agency for Toxic Substances and Disease Registry (ATSDR, 1989) has reviewed several *in vitro* genotoxicity studies on mercury compounds. Mercuric chloride was found to induce gene mutations in mouse lymphoma cells (Oberly et al., 1982) and DNA damage in rat and mouse fibroblasts (Zasukhina et al., 1983). It was observed to 1983; Christie et al., 1986). Using the alkaline elution assay in intact Chinese hamster ovary cells, several studies have shown that mercuric chloride can cause single-strand breaks in DNA (Cantoni et al., 1982, 1984a, 1984b; Cantoni & Costa, 1983; Christie et al., 1984, 1986). Furthermore, Cantoni & Costa (1983) found that the

DNA-damaging effect of mercuric chloride is enhanced by a concurrent inhibitory effect that mercury has on DNA repair mechanisms.

8.5. Carcinogenicity

WHO (1976) reported no evidence that inorganic mercury is carcinogenic. In a study by Schroeder & Mitchener (1975), groups of mice were exposed to various metals, including mercuric chloride. After a lifetime of exposure to 5 µg mercury/litre in basal drinking-water, 51.2% (21 out of 41) of the mice revealed tumours compared to 29.8% (14 out of 47) among controls. The incidence was higher than for any of the other metals tested, but the authors concluded that no element was significantly tumorigenic. Mercury has not been reviewed by IARC (IARC, 1987). The US EPA (1989) has classified inorganic mercury as a group O compound, i.e. it is not classifiable as to human carcinogenicity.

8.6. Factors modifying toxicity

Factors such as age, sex, nutritional state, and oral exposure giving rise to sensitization are likely to affect the relationship between dose and effect or response. The type of chemical exposure (whether to elemental mercury or to mercuric mercury salts) is an important determinant for the toxic effect and to differences in distribution.

As described in section 6.1.2, Kostial et al. (1978) observed a high degree of absorption of inorganic mercury in newborn rats after oral exposure to mercuric chloride. The immature rodent kidney is, on the other hand, less sensitive to mercury exposure than the adult kidney, as less accumulation takes place in the kidney of the newborn pups (Daston et al., 1983). No information is available concerning age effects in humans.

Exposure of rats to high concentrations of mercury vapour induced metallothionein in kidney tissue that resulted in the binding of divalent mercury (Sapota et al., 1974). Female rats are less susceptible than male rats to the nephrotoxic effect of mercuric mercury (Magos et al., 1974). This seems to be related to the metallothionein content of the kidney, which is higher in females and is increased by estradiol treatment (Nishiyama et al., 1987). Administration of zinc to rats reduced the renal toxic effects of mercuric mercury and induced an increase in the glutathione (Fukino et al., 1986) and metallothionein content of renal tissue (Yoshikawa & Ohta, 1982). Zinc treatment in hamsters injected with mercuric salt reduced the embryotoxic and teratogenic effects produced by treatment with the mercuric salt alone (Gale, 1984).

Selenium has been found to affect the distribution of mercuric mercury in rats (Parizek & Ostadalova, 1967; Nygaard & Hansen, 1978), mice (Eybl et al., 1969), rabbits (Imura & Naganuma, 1978; Naganuma & Imura, 1980), and pigs (Hansen et al., 1981). As a consequence of this redistribution, a decrease in toxicity has also been observed (Parizek & Ostadalova, 1967; Johnson & Pond, 1974). Mercury forms a mercury-protein complex with selenium (Burk et al., 1974), which can be identified in plasma and blood cells (Chen et al., 1974; Imura & Naganuma, 1978). When given with selenium, mercury is retained longer in blood and, as a consequence, accumulation in the kidney is decreased. Mercury taken up by the kidney is bound to a protein-selenium complex, and, on administration of equivalent amounts of selenium, the binding to metallothionein is diminished and may be negligible (Komsta-Szumska & Chmielnicka, 1977; Mengel & Karlog, 1980). A consequence of the changed binding of mercury in blood brought about by selenium is that transport of selenium and mercury through the placenta membranes is inhibited (Parizek et al., 1971).

So far only selenate or selenite compounds, and not the naturally occurring selenium compounds in food, have been studied in detail. However, Magos et al. (1984, 1987) compared the distribution and form of mercury and protection against the nephrotoxic effects of mercury after exposure to different forms or compounds of selenium. It was concluded that dietary selenium is less efficient than selenite as an antidote against mercurial nephrotoxicity.

Studies of selenium interaction with mercuric mercury have mainly been carried out in rodents. Selenium metabolism in humans is different from that in most animals, and selenium dependency in humans is comparatively less than that in rodents. However, observations in workers exposed to mercury vapour indicate that there is also a selenium-mercury interaction in humans. Selenium and mercury concentrations with a molar ratio of 1:1 have been found in organs such as the brain, thyroid, and pituitary (Kosta et al., 1975; Rossi et al., 1976). In renal biopsies from two mercury-intoxicated patients, inclusion bodies were seen in lysosomes of renal tubules, and it was demonstrated that these inclusion bodies contained selenium and mercury (Aoi et al., 1985). In 28 workers exposed to mercury vapour, the selenium excretion in urine was high compared to non-exposed workers (Alexander et al., 1983). However, this was not confirmed by Suzuki et al. (1986), who studied 57 workers exposed to mercury vapour. They found a decrease in selenium excretion as mercury excretion in the urine increased.

As discussed in section 6.2, ethanol inhibits the enzyme catalase, which is the main enzyme responsible for the oxidation of mercury in blood and tissues. Ethanol

consumption thus modifies the balance between oxidation and reduction of mercury in tissues. As a consequence, less mercury vapour is absorbed from the lungs, more mercury exists unoxidized in the blood, and more mercury is transported to the brain. It is unclear whether the observed decrease of mercury in the brain is due to the fact that less mercury is oxidized and retained in the brain or that more retained mercury is lost from the brain as a result of reduction following the intake of ethanol. The mercury content of the brain following acute exposure to mercury in acatalasaemic mice is greater than that of mercury-exposed control mice (Ogata et al., 1987). This is also the case with the fetal brain after exposure of pregnant female acatalasaemic mice (Ogata & Meguro, 1986).

8.7. Mechanisms of toxicity - mode of action

The neurotoxic effect seen after exposure to metallic mercury vapour is attributable to the divalent mercury ion formed through oxidation in the brain tissue. Interference with enzyme function by binding to sulfhydryl groups is one possible mechanism. Kark (1979) reviewed the available evidence regarding the inhibitory effect of mercuric ions on different enzyme systems (*in vitro* and *in vivo).* Mercury concentrations at which enzyme inhibition appears are consistent with concentrations at which toxic effects on the central nervous system are observed. The *in vivo* conditions are, however, complicated. Ligands capable of binding mercuric ions, e.g., sulfhydryl groups and selenohydrol groups, are ubiquitous and associated with proteins. These ligands may have a protective or scavenging effect, thereby preventing interference with important

receptors. Mercuric ions penetrate cell membranes to a very limited degree. In contrast mercury vapour penetrates more readily due to its lipophilicity. Miyamoto (1983) demonstrated with frog nerve-muscle preparations that mercuric mercury penetrates the nerve cell membrane through sodium and calcium channels, causing an irreversible depolarization and an increase in transmitter release. There is a subsequent irreversible block of transmitter release. Transport through the cell membrane via the formation of carrier complexes would also be a possibility, although this has not been demonstrated. Mercury has been found intracellularly in nerve cells after exposure to mercury vapour (Cassano et al., 1966) and also after prolonged exposure to mercuric chloride in the rat (Moller-Madsen & Danscher, 1986).

Mercuric ions react with DNA and RNA *in vitro* and may change the tertiary structure of these molecules (Eichhorn & Clark, 1963; Gruenwedel & Davidson, 1966). Inhibition of protein synthesis has been observed in cell systems as well as in cell-free systems at a mercury concentration equivalent to 2×10^{-5} mol/litre (Nakada et al., 1980). Similar mercury concentrations have been observed to

increase the pre-synaptic release of the transmitter substance acetylcholine (Kostial & Landeka, 1975; Manalis & Cooper, 1975). An increase in the release of dopamine in the rat brain after treatment with mercury (10^{-5} mol per litre) at a level of 2 µg/g was observed by Bondy et al. (1979).

Mercury may interfere with membrane structure *in vitro* by hydrolysing specific lipids (Ganser & Kirschner, 1985), causing membrane lesions, and by reducing lipid synthesis in nerve cells (Cloez et al., 1987). Furthermore, an irreversible interference with the post-synaptic membrane has been observed (Manalis & Cooper, 1975; Juang, 1976).

Knowledge regarding the mechanism of mercury neurotoxicity, following exposure to mercury vapour, is still fragmentary. Little data has so far emerged concerning morphological changes in the human or primate brain. Mercury has been demonstrated in rats within the motor nuclei of the rhombencephalon and the cerebral cortex, the highest concentrations occurring in striated areas and within the deep nuclei of the cerebellum. A proportionately high level was seen in the anterior horn motor neurones of the spinal cord. The localization was generally interneuronal, but was also seen in the cytoplasm of glial and ependymal cells (Moller-Madsen & Danscher, 1986). In human cases of mercury poisoning, chromatolysis in scattered neurones was observed in the occipital lobe of the brain and there was a loss of Purkinje cells (Takahata et al., 1970). Davis et al. (1974) demonstrated, in two human cases, mercury in the cytoplasm of neurones in the nuclei olivaris and dentatus, in Purkinje cells,

in anterior horn cells of the spinal cord, and in the neurones of the substantia nigra. In both cases a decrease in the number of neurones of the granular cell layer in the cerebellum and, possibly, also of Purkinje cells was seen.

The mechanism behind the nephrotoxic effect of inorganic mercury is discussed in sections 8.2 and 9.3. Here it can be summarized that two types of renal injury have been observed. The first is a glomerular injury caused by an auto-immune reaction induced by mercury and resulting in antibody formation against the glomerular tissue, deposition of immune complex, glomerular nephritis, proteinuria, and nephrotic syndrome. Alternatively, immune complexes containing other mercury-induced anti-bodies may be deposited in the glomeruli. The second is a renal tubular damage affecting the proximal tubules and developing in parallel with the accumulation of mercury in the renal tubular cells. This damage results in a loss of renal tubular enzymes, such as gamma-glutamyl transferase, and lysosome enzymes, such as beta-galactosidase, beta-glucuronidase and *N*-acetyl-beta-glucosaminidase (Foa et al.,

1976), and in decreased reabsorption leading to an increased secretion of endogenous trace elements such as zinc and copper (Chmielnicka et al., 1986). An early effect is an inhibition of protein synthesis. A swelling of the endoplasmic reticulum with disaggregation of polyribosomes is observed in electron microscopy. Eventually, renal tubular necrosis and renal failure develop (Wessel, 1967; Gritzka & Trump, 1968; Barnes et al., 1980; Pezerovic et al., 1981).

The immunotoxic effect of inorganic mercury is probably the least understood effect of exposure to inorganic mercury. Mercuric mercury has been observed as a potent stimulator of human T lymphocytes *in vitro* (Schöpf et al., 1969; Nordlind & Henze, 1984; Nordlind, 1985). Mercury is initially bound to lymphocyte membranes, but it has also been demonstrated that there is an uptake of mercury by the nuclei (Nordlind, 1985) at levels likely to occur in blood following exposure to mercury vapour. It can be speculated that this phenomenon may be related to the rather generalized syndromes observed in children, such as acrodynia or "Pink disease" (Warkany, 1966; Skerfving & Vostal, 1972) and the rather generalized and unspecific syndromes reported to be related to dental amalgam fillings, but with an unproven relation to mercury exposure (section 9.7).

9. EFFECTS ON HUMANS

WHO (1976) dealt primarily with effects of occupational exposure to mercury vapour. Apart from accidental exposure, there was little information on exposure to inorganic mercury among the general population. Recent data indicate that the release of mercury vapour from amalgam

fillings may dominate exposure to inorganic mercury among
the general population (Elinder et al., 1988; WHO, 1990).
Other sources are a fish-rich diet (biotransformation of
alkyl mercury present in some species of fish resulting in
the accumulation of inorganic mercury), environmental pol-
lution in the vicinity of industrial sources, toxic waste
sites, and accidental spillage. Mercury-containing phar-
maceuticals may also be significant sources of exposure
for some populations.

    The present review will focus on possible chronic
effects of long-term, low-level occupational exposure and,
for the general population, of mercury released from
amalgam. However, a brief review of acute effects will be
given. In general, the available information is presented
according to the effects on organs or organ systems. Some-
times this is not possible, as is the case for the combi-
nation of a number of unspecific symptoms that have been
associated by some with exposure from dental amalgams.
Whenever dose-response relationships are discussed, it
should be borne in mind that data on exposure levels in
the past are scarce. Quality assurance data are with few
exceptions not reported. In most studies personal samplers
were not used but only static samplers, which can be a
source of considerable error in the estimated absorbed
dose, as demonstrated by Stopford et al. (1978) and Roels
et al. (1987).

    Data related to response rates are sometimes difficult
to interpret. The studies are as a rule cross-sectional,
and so selection bias, which may lead to either an under-
estimation or an overestimation of risks, can occur. The
numbers of exposed subjects and controls are often small.
For quite a few of the parameters studied, the results may
be influenced by the investigator and "interviewer bias"
is thus possible.

9.1. Acute toxicity

    Workers acutely exposed (4-8 h) to calculated elemen-
tal mercury levels of 1.1 to 44 mg/m^3 due to an accident
exhibited chest pains, dyspnoea, cough, haemoptysis,
impairment of pulmonary function, and evidence of inter-
stitial pneumonitis (McFarland & Reigel, 1978). Acute mer-
cury poisoning with mercurial pneumonitis was reported
among four men after they were exposed to mercury vapour
while attempting home gold ore purification using a gold-
mercury amalgam and sulfuric acid (Levin et al., 1988).

Urine mercury levels were 169 to 520 µg/litre   in two
cases. Probably there was also substantial exposure to
sulfur dioxide and sulfuric acid.

    Troen et al. (1951) reported 18 cases of human poison-
ing following oral ingestion of single doses of mercuric
chloride, nine of which resulted in death. The lethal
doses ranged from 29 mg/kg body weight to at least

50 mg/kg. The most common autopsy findings in these cases
were gastrointestinal lesions (ranging from mild gastritis
to severe necrotizing ulceration of the mucosa) and renal
lesions that had resulted in renal failure.

9.2. Effects on the nervous system

Most information focuses on effects on the central
nervous   system following occupational   exposure. The
central nervous system is the critical organ for mercury
vapour exposure (WHO, 1976). Acute exposure has given rise
to psychotic reactions characterized by delirium, halluci-
nations, and suicidal tendency. Occupational exposure has
resulted in erethism, with irritability, excitability,
excessive shyness, and insomnia as the principal features
of a broad-ranging functional disturbance. With continuing
exposure, a fine tremor develops, initially involving the
hands and later spreading to the eyelids, lips, and
tongue, causing violent muscular spasms in the most severe
cases. The tremor is reflected in the handwriting which
has a characteristic appearance. In milder cases, erethism
and tremor regress slowly over a period of years following
removal from exposure. Decreased nerve conduction velocity
in mercury-exposed workers has been demonstrated (Bidstrup
et al., 1951).   Long-term, low-level exposure has been
found to be associated with less pronounced symptoms of
erethism, characterized by fatigue, irritability, loss of
memory, vivid dreams, and depression (WHO, 1976).

9.2.1. Relations between mercury in the central nervous system and effects/response

There is very little information on brain mercury
levels in cases of mercury poisoning, and nothing that
makes it possible to estimate a no-observed-effect level
or a dose-response curve. Furthermore, the available data
are uncertain as they are not accompanied by analytical
quality control information.

Brigatti (1949) reported mercury concentrations of
6-9 mg/kg in the brain of two workers exposed to mercury
vapour and with signs of mercury poisoning 2 years before
they died. In two similar cases, Takahata et al. (1970)
reported 5-34 mg mercury/kg in different parts of the
brain. In two fatal cases of poisoning, which followed
many years of exposure to high doses of calomel as a
laxative, mercury concentrations of about 4 mg/kg in the
frontal lobe cortex were reported, and in one of the cases

a concentration of 106 mg/kg was found in the inferior
olive (Davis et al., 1974; Wands et al., 1974). The symp-
toms were dementia, erethism, colitis, and renal failure.
A dose of two tablet laxatives, each containing 120 mg of
USP-grade mercurous chloride, had been taken daily for 25
years in one case and for 6 years in the other.

9.2.2. Relations between mercury in air, urine or blood and

effects/response

9.2.2.1 Occupational exposure

WHO (1976) found no evidence of the classical symptoms of mercurialism, erethism, intentional tremor, or gingivitis below a time-weighted occupational exposure to mercury in air of 100 µg/m^3. A report on cottage industry mercury smelting in China (Wu et al., 1989) has confirmed the classical symptoms at exposure levels of up to 600 µg/m^3. Symptoms such as loss of appetite and psychological disturbance have also been found to occur at mercury levels below 100 µg/m^3 (WHO, 1976).

Zeglio (1958) observed that following cessation of exposure, symptoms and signs of neurological impairment regress slowly in the milder cases of poisoning affecting the nervous system. However, in the more severe cases, neurological impairment persists and may become exacerbated.

One of the studies on which WHO (1976) based its conclusions was carried out by Smith et al. (1970). This study covered the prevalence of several medical findings in 567 workers in a number of chloralkali factories in the USA in relation to mercury vapour exposure (Fig. 6). The authors concluded that the data showed no significant signs or symptoms in persons exposed to mercury vapour at or below a level of 0.1 mg/m^3. Subjective symptoms appeared to increase at lower exposure levels, but the authors questioned this finding because of the confounding effect of alcohol. In a follow-up of part of this study, Bunn et al. (1986) did not find significant differences in the frequency of objective or subjective findings related to mercury exposure, which generally was said to range from 50 to 100 µg/m^3 (time-weighted average). The report, however, did not give sufficient information about several methodological questions, including quality assurance aspects and possible confounding variables.

Later studies, covering industries where exposure has been high, have pointed towards the importance of urine mercury peaks in excess of 500 µg/litre for the development of neurological signs and symptoms (Langolf et al., 1978, 1981). Urine mercury peaks in excess of 100 µg per litre have been associated with impaired performance in mechanical and visual memory tasks and psychomotor ability tests (Forzi et al., 1976).

There is also a report (Albers et al., 1988) that, as long as 20 to 35 years after exposure, subjects who had experienced urine mercury peak levels above 600 µg per litre demonstrated significantly decreased strength, decreased coordination, increased tremor, decreased sensation, and increased prevalence of Babinski and snout reflexes when compared with control subjects. Furthermore, subjects with reported clinical polyneuropathy had sig-

nificantly higher peak levels of mercury in urine than the subjects without those signs. The reported signs of the presence of an upper motor neuron lesion will require further investigation. Many measures demonstrating significant differences between exposed and unexposed subjects were age dependant, but a multiple regression analysis showed that the association between neurological signs and mercury exposure remained after allowing for age (Albers et al., 1988).

Relation between mercury in work room and certain signs and symptoms (From: Smith et al., 1970).
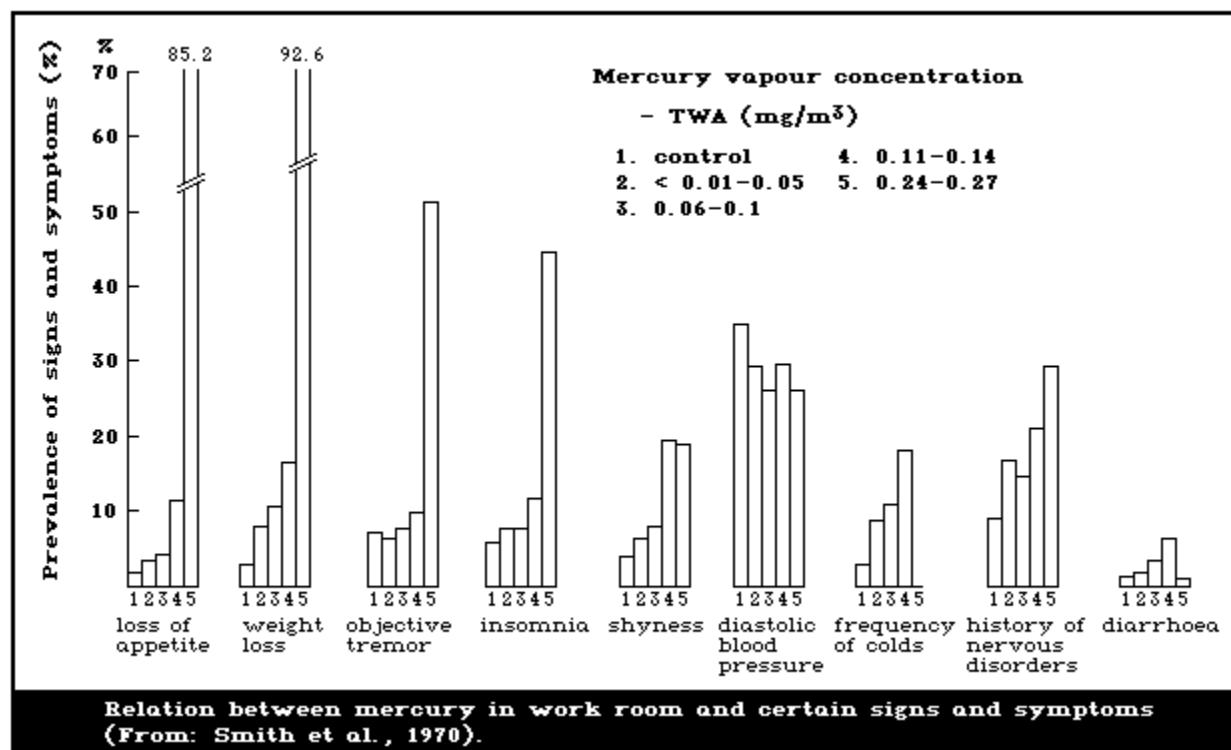
Several reports address studies where the investigators have looked into possible effects at much lower exposure levels. In a study of 142 exposed and 65 control subjects, Miller et al. (1975) examined subclinical effects related to exposure to inorganic mercury in the chloralkali industry and in a factory for the manufacture of magnetic materials. Mercury levels in urine varied from normal to over 1000 µg/litre. Neurological examination found evidence of eyelid fasciculation, hyperactive deep tendon reflexes and dermatographia, but these findings did not correlate with urinary mercury levels or length of

exposure. However, a power spectral analysis of forearm tremor, by which it was possible to quantify tremor frequency distribution and amplitude, showed a significant increase in average tremor frequency with elevated urinary mercury level. An effect was observed at urine concentrations above about 50 µg/litre.

Roels et al. (1982) studied psychomotor performance in workers in a chloralkali plant and a factory for the manu-

facture of electric batteries. The results suggested that preclinical psychomotor dysfunction related to the central nervous system occurs when blood mercury levels rise to values between 10 and 20 µg/litre and when mercury in urine exceeds 50 µg/g creatinine. However, even in a subgroup with urinary mercury levels below 50 µg/g creatinine, some parameters differed from those of a control group.

In a further study, Roels et al. (1985) examined 131 male workers and 54 female workers exposed to metallic mercury vapour in various Belgian factories. The controls used were 114 non-exposed male workers and 48 female workers. The subjects in the control and exposed groups were closely matched with respect to age, weight, and height. Also several other confounding factors were kept under control. One criterion for the inclusion of exposed workers was that they should have been uninterruptedly exposed to mercury vapour for at least 1 year prior to the study. A large number of questions were asked in order to detect symptoms mainly related to nervous system disturbances. A self-administered questionnaire, which was completed the next day by the examiner, was the basis for this information. A large number of CNS tests were used, such as reaction time, flicker fusion, colour discrimination, short-term memory, and hand tremor. Mercury was measured in urine and blood. Renal function was studied using various tests, including total protein and beta-2-microglobulin in blood and urine, and retinol-binding protein, albumin, and the lysosomal enzyme beta-galactosidase in urine. Several symptoms mainly related to the central nervous system (memory disturbances, depressive feelings, fatigue, irritability) were more prevalent in the exposed subjects than in the controls. The means and 95 percentiles for urine mercury levels in non-exposed and exposed subjects were, respectively, 52 and 147 µg/g creatinine for males and 37 and 63 µg/g creatinine for females. The symptoms were, however, not related to exposure parameters. The authors therefore considered it possible that the reporting of these symptoms was influenced by knowledge of exposure to mercury vapour. There were no significant disturbances in short-term memory, simple reaction time, critical flicker fusion, and colour discrimination ability that were related to the mercury exposure. However, an effect on hand tremor was observed in males. The prevalence was 5% in the non-exposed group

and 15% in the exposed group. Duration of exposure seemed to be more important than exposure intensity, but an increased prevalence of tremor was apparent in both the groups with the lowest exposure (urine mercury level of 5-50 µg/g creatinine) and that with the shortest exposure duration (1-4 years).

Among 26 workers exposed to mercury vapour in a chlor-alkali plant or in the production of fluorescent tubes and acetaldehyde, there was an increased incidence of reports

of hand tremor, compared with a control group (Fawer et al., 1983). The exposure, based on personal air sampling, was on average only 26 µg/m^3. The mean urine concentration was 20 µg/g creatinine (11.3 µmol/mol creatinine). Similar results were reported in a study by Verberk et al. (1986), where 21 workers in a fluorescent lamp production factory were examined. The excretion of mercury in urine varied between 15 and 95 µg/g creatinine, the average value being 35 µg/g creatinine. No control group was examined, but with increasing exposure effects were seen in several tremor parameters. The effects were reported to occur irrespective of cigarette or alcohol consumption or age.

Piikivi et al. (1984) reported decreased verbal intelligence and memory in a group of 36 chloralkali workers compared with a control group. Such effects were seen more frequently in a subgroup where the urine mercury level was above 56 µg/litre than in a subgroup where levels were below this value. Piikivi & Hänninen (1989) made refined analyses of the results of another study on 60 chloralkali workers and matched controls. The exposed workers had an average urine mercury concentration of 84.1 nmol/litre. Neither the perceptual-motor, memory, nor learning abilities of the mercury-exposed workers showed any disturbances when compared to the controls. However, the exposed workers reported statistically significantly more disturbances of memory than the controls. According to multivariate analysis of variance, the memory disorders were significantly associated with the form of workshift but not with the level of exposure. In a further study (Piikivi & Tolonen, 1989), EEG changes were found in a group of 40 workers, compared to matched controls, after several years of exposure to an average metallic mercury vapour level of about 25 µg/m^3 air, corresponding to a urine mercury level of about 20 µg/litre. The EEG was significantly slower and more attenuated in exposed workers.

Results from the studies of Schiele et al. (1979), Triebig et al. (1981), and Triebig & Schaller (1982) indicate effects on cognitive functions and memory. However, it is not possible to draw conclusions concerning dose-response relationships from these studies. In a study by Schuckmann (1979), 39 chloralkali workers with an average

urinary mercury concentration of about 100 µg/litre were compared with a control group. There was no evidence of changes in psychomotor activity. Smith et al. (1983) studied effects on short-term memory in one group of 26 male chloralkali workers with an exposure corresponding to urine mercury levels averaging 195 µg/litre and one group of 60 male workers where the average urine mercury level was 108 µg/litre. The severity of the effects was found to be related to the intensity of mercury exposure.

There are some reports (Levine et al., 1982; Shapiro

et al., 1982; Singer et al., 1987; Zampollo et al., 1987)
that elemental mercury vapour causes peripheral neuropathy
at urinary levels of 50-100 µg/litre. Levine et al.
(1982) found a dose-response relationship between urine
mercury concentrations above 50 µg/litre and nerve con-
duction tests.

9.2.2.2 General population exposure

The exposure of the general population is typically
low, but occasionally may be raised to the level of occu-
pational exposure and can even result in adverse health
effects. Thus mishandling of liquid mercury, mercury
dispersed from jars, broken thermometers, fluorescent
lamps, and ingestion of mercury batteries have resulted in
severe intoxication and occasionally acute pneumonitis.
Children of mercury workers can also be exposed to mercury
vapour from contaminated work clothes. Hudson et al.
(1987) reported considerable mercury exposure among
children of mercury workers from a thermometer plant. The
median urine mercury level of 23 workers' children was
25 µg/litre compared with a value of 5 µg/litre among
39 controls. Three of the workers' children had urine mer-
cury levels above 50 µg/litre; one was above 100 µg per
litre. Mercury levels in workers' homes had a median
value of 0.24 µg/m^3 compared with 0.05 µg/m^3 in
non-workers' homes. No signs of mercury intoxication were
reported, based on a questionnaire to parents and on a
neurological examination that included assessment of
tremor by spectral power analysis. Urine protein was
measured only by dipstick. The reported air mercury levels
do not explain the high urinary concentrations. There must
have been exposure from sources that were not identified,
e.g., clothes. It is not known what measures were taken
to avoid contamination of sampling bottles.

Children who are exposed to mercury vapour from
interior latex paint may develop acrodynia. In 1989, a
4-year-old boy developed severe acrodynia 10 days after
the inside of his home was painted with 64 litres of
interior latex paint containing 945 mg mercury/litre. He
sequentially developed leg cramps, a generalized rash,
pruritis, sweating, tachycardia, an intermittent low-grade
fever, marked personality change, erythema and desqua-
mation of the hands, feet, and nose, weakness of the

pelvic and pectoral girdles, and lower extremity nerve
dysfunction. The level of mercury in a 24-h collection of
urine was 65 µg/litre.

9.3. Effects on the kidney

The kidney is the critical organ following the inges-
tion of inorganic bivalent mercury salts. Oliguria,
anuria, and death from renal failure resulting from acute
tubular necrosis has occurred not infrequently in the past
following the ingestion of mercuric chloride either acci-

dentally or with suicidal intent, and such cases have also
followed therapeutic administration of mercurials. At the
other extreme, organic mercurials have until recent years
been used extensively in medical practice as effective
diuretics in the management of congestive cardiac failure.
Occupational exposure to metallic mercury has for long
been associated with the development of proteinuria, both
in workers with other evidence of mercury poisoning and in
those without such evidence. An increased prevalence of
proteinuria in mercury workers, compared with a control
group, and a significant correlation between urinary mer-
cury excretion and protein excretion have been demon-
strated (Joselow & Goldwater, 1967). Less commonly, occu-
pational exposure has been followed by the nephrotic
syndrome (Kazantzis et al., 1962). Such cases have also
followed the therapeutic administration of mercurials,
although the role of mercury in some of these reported
cases, where other etiological factors may have been oper-
ative, is less clear. Two children developed the nephrotic
syndrome following a spillage of mercury in their bedroom
from a broken thermometer (Agner & Jans, 1978). The cur-
rent evidence suggests that the nephrotic syndrome follow-
ing absorption of mercury compounds results from an
immunotoxic response.

9.3.1. Immunological effects

    WHO (1976) stated that effects of elemental mercury
vapour on the kidney had been reported only at doses
higher than those associated with the onset of CNS signs
and symptoms. Since then several new studies have been
carried out, and kidney effects have been seen at lower
exposure levels. Simultaneously, experimental studies on
animals have shown that inorganic mercury may induce
auto-immune glomerulonephritis in all species tested but
not in all strains, indicating a genetic predisposition.

    Kazantzis (1978) and Filliastre et al. (1988) reviewed
the role of hypersensitivity and the immune response in
influencing susceptibility to metal toxicity, and gave
evidence of several case histories of clinical kidney
disease after exposure to mercury, occupationally as well
as among the general population. Of 60 adult African women
using skin-lightening creams containing inorganic mercury,

26 developed the nephrotic syndrome (Barr et al., 1972).
Kibukamusoke et al. (1974) reported one case of membranous
nephropathy, due to the use of skin-lightening cream,
where immunofluorescence showed finely granular IgG, IgM,
and C3 complement deposits. IgG and C3 complement deposits
were reported also by Lindqvist et al. (1974) in eight
cases with nephrotic syndrome. The authors also observed
similar kidney changes in two rabbits after application
(3 times per week for more than three months) of skin-
lightening cream to the skin area between the ears.   The
rabbits developed proteinuria and died.

9.3.2. Relations between mercury in organs and effects/response

    Only very limited information is available. In the
report by Davis et al. (1974) referred to in section
9.1.1, kidney mercury concentrations of 422 mg/kg and
25 mg/kg were measured in two fatal cases of poisoning.
However, no information was given on whether or not
adverse effects on the kidney were observed.

9.3.3. Relations between mercury in air, urine and/or blood
and effect/response

    Foa   et al. (1976) examined chloralkali industry
workers exposed to mercury vapour concentrations of 0.06
to 0.3 mg/m^3.   There were 15 cases of glomerular protein-
uria among 81 workers examined. Increased levels of
certain lysosomal enzymes were found in plasma, and this
effect was observed even in a group where the average
urine mercury level was only 35 µg/litre.

    Stewart et al. (1977) examined 21 laboratory assist-
ants exposed not only to metallic mercury vapour but also
to mercuric mercury and formaldehyde and found increased
urinary excretion of protein. Air concentrations of mer-
cury were 10-50 µg/m^3,   and the median urine mercury
excretion rate was 53 µg/24 h (about 35 µg/litre urine).
Preventive measures were taken and in a follow-up study of
nine subjects one year later there was no evidence of
proteinuria.

    Buchet et al. (1980) examined a group of 63 workers in
a chloralkali plant and found, compared with a control
group, increased plasma and urinary concentrations of the
enzyme beta-galactosidase, increased urinary excretion of
proteins with high relative molecular mass, and slightly
increased beta-2-microglobulin concentration in the plasma
without a concomitant increase in urinary concentration.
The urinary excretion of transferrin, albumin, and
beta-galactosidase was significantly correlated with the
urine concentration of mercury. The likelihood of finding
effects increased in workers with urine and/or blood mer-
cury concentrations of over 50 µg/g   creatinine or
30 µg/litre   blood. The data indicated an increased con-
centration of beta-galactosidase even in the group of

workers with an average urine mercury concentration of
about 20 µg/g creatinine. According to the authors the
results suggest that mercury vapour exposure may lead to a
slight glomerular dysfunction in some workers, and their
hypothesis is that the glomerular dysfunction is a result
of an auto-immune reaction.

    The same research group (Roels et al., 1982) studied
the prevalence of proteinuria among 43 workers exposed to
metallic mercury vapour (median urine and blood mercury
levels of 71 µg/g creatinine and 21 µg/litre, respect-
ively) in two other factories (section 9.2.2). Increased

total proteinuria and albuminuria was slightly more preva-
lent in the mercury-exposed group than in the control
group.

No evidence of renal dysfunction (proteinuria, albumi-
nuria, retinol-binding proteins, aminoaciduria, creati-
nine, and beta-2-microglobulin in serum) was found among 62
exposed workers in a chloralkali plant and a zinc-mercury
amalgam factory, compared with a control group (Lauwerys
et al., 1983). The mean urine mercury concentration in the
exposed group was 56 µg/g creatinine. In eight exposed
workers, but in none of the controls, antibodies against
laminin, a non-collagen glycoprotein in the glomerular
basal membrane, were found. However, in a later study of
workers in another chloralkali plant and in a battery fac-
tory (Bernard et al., 1987), the prevalence of circulating
anti-laminin antibodies was not increased.

Stonard et al. (1983) examined a group of about 100
chloralkali industry workers with an average urine mercury
level of 67 µg/g creatinine. They found no evidence of
renal dysfunction and no increased excretion of proteins.
An increase in circulating immune complexes was found but
there were no anti-glomerular basement membrane antibodies
in the serum.

Roels et al. (1985) examined the renal function of 185
workers exposed to metallic mercury vapour (see also
section 9.2.2.1). Slight tubular effects were detected in
both male and female workers, in the form of an increased
urinary beta-galactosidase activity and an increased urinary
excretion of retinol-binding proteins. The effects were
dose related. Some increase in the prevalence of abnormal
values was seen even at mean urine mercury levels of about
30 µg/g creatinine. However, there was not, as was the
case for tremor, a dose-response relationship concerning
the length of the exposure period.

Rosenman et al. (1986) reported that urinary
N-acetyl-beta-glucosaminidase (NAG) enzyme levels increased
with increasing urine mercury levels over the range of
100-250 µg/litre. In a study of chloralkali industry

workers, there was a slight increase in the urine NAG con-
centration among exposed workers (average urine mercury
level of 50 µg/litre), compared with a control group
(Langworth, 1987).

Another way of studying kidney effects is to measure
the brush-border protein (BB-50) concentration in the
urine. This indicates the loss of organic tissue rather
than functional changes in the kidney cells. The urinary
BB-50 concentration was studied in 40 workers, with an
average urine mercury concentration of 46 µg/g creati-
nine and who were exposed for an average of 7 years (Mutti
et al., 1985), and 36 matched control workers. There was
no difference between exposed and non-exposed workers in

average urinary albumin or retinol-binding protein. How-
ever, when the 20 workers with urinary mercury above
50 µg/g   creatinine were analysed separately, a shift of
the BB-50 distribution towards higher values was found by
a chi-square test (p = 0.07).

A study of 509 infants exposed to phenylmercury from
contaminated diapers (Gotelli et al., 1985) showed a clear
dose-response relationship between inorganic mercury in
urine and urinary excretion of gamma-glutamyl transpeptidase,
an enzyme in the brush borders of the renal tubular cells.
Since phenylmercury compounds are known to be rapidly
degraded to inorganic mercury in animals (Magos et al.,
1982), it is likely that the renal effect in the infants
was caused by inorganic mercury. Apart from the increased
enzyme excretion, the children with the highest exposure
also had increased 24-h urine volume. The enzyme excretion
increased at a urine mercury excretion of 4 µg/kg   body
weight and the urine volume increased at 14 µg/kg   body
weight.

9.4. Skin reactions

9.4.1. Contact dermatitis

Primary hypersensitivity to metallic mercury is con-
sidered rare (Burrows, 1986). However, Thiomersal (sodium
ethylmercurithiosalicilate) and ammoniated mercury have
been found to be common sensitizers in a survey on the
epidemiology of contact dermatitis (North American Contact
Dermatitis Group, 1973), Thiomersal being the third com-
monest sensitizer (after nickel and chromium) in the gen-
eral population. Both aryl- and alkylmercurial seed dress-
ings have also been shown to be potent skin sensitizers.
Mercury compounds give rise to a type IV cell-mediated
delayed hypersensitivity reaction (Coombs & Gell, 1975).

There have been a few cases of allergic dermatitis
among dental personnel (White & Brandt, 1976; Rudzki,
1979; Ancona et al., 1982). Patch testing of dental

students (White & Brandt, 1976) indicated that the preva-
lence rate of mercury hypersensitivity increased by class
from prefreshmen to seniors, successive values being 2.0%,
5.2%, 4.1%, 10.3%, and 10.8%. However, in a subsequent
study (Miller et al., 1987), similar results were not
found, but positive results from patch testing increased
in relation to the number of amalgam restorations in the
students. The overall percentage of positive reactions to
mercuric chloride was very high (32%), which may indicate
methodological problems. In this study, as in the study of
White & Brandt (1976), the patch testing was carried out
with 0.5 ml of a 0.1% aqueous solution of mercuric chloride.

Symptoms have occasionally been reported to relate to
amalgam fillings (Frykholm, 1957; Thomson & Russell, 1970;
Duxbury et al., 1982; SOS, 1987). In most cases the main

symptoms were facial dermatitis, sometimes with erythematous and urticarial rashes. Symptoms from the mouth (oral lichen planus) occasionally occurred. The symptoms started a few hours after the insertion of amalgam. Nakayama et al. (1983) reported 15 cases of generalized dermatitis caused by mercury after exposure from broken thermometers or dental treatment. In another very recent study employing epicutaneous testing, positive mercury hypersensitivity reactions were confined to subjects having pre-existing amalgam restorations (Stenman & Bergman, 1989).

Finne et al. (1982) performed patch tests on 29 patients with amalgam fillings and oral lichen planus. Contact allergy was found in 62% of the subjects, compared with 3.2% in a control group. In four of the patients, all the amalgam restorations were removed and replaced by gold and composite materials. The lesions healed completely in three of these patients after an observation period of one year, and in the remaining case there was considerable improvement.

When peripheral blood lymphocytes from non-atopic subjects were cultured in the presence of pokeweed mitogen and mercuric chloride, a significant enhancement of the production of total IgE was observed, whereas the production of IgM and IgA remained unaffected (Kimata et al., 1983).

9.4.2. Pink disease and other skin manifestations

In the 1940s, "Pink disease" (acrodynia) was reported in children below 5 years of age as a result of the use of mercurous chloride in teething powder and ointments. Affected children became irritable and generally miserable and had difficulty in sleeping. Profuse sweating, photophobia, and generalized rash followed. The extremities became cold, painful, red, and swollen, and the skin desquamated. Neither the occurrence of this disease nor its severity was dose related. The urinary

excretion of mercury in affected children was elevated but below the toxic level. After the withdrawal of teething powder preparations by the main United Kingdom manufacturers in 1953, there was a dramatic decline in the occurrence of Pink disease. Calomel is not the only mercurial that can cause Pink disease. Mercury dispersed from broken fluorescent bulbs (Tunnessen et al., 1987), long-term injection of gamma-globulin preserved with ethylmercurithiosalicylate (Matheson et al., 1980), and the use of nappies treated with phenylmercury (Gotelli et al., 1985) have also been responsible for Pink disease. Exposure to mercury vapour may be associated with the mucocutaneous lymph node syndrome or "Kawasaki disease", which has many similarities with Pink disease (Orlowski & Mercer, 1980). Although the pathogenesis of Pink disease and Kawasaki disease is unknown, there is good evidence that Kawasaki disease is immunologically mediated, increased serum IgE

concentrations and eosinophilia having been reported
(Kusakawa & Heiner, 1976; Orlowski & Mercer, 1980; Adler
et al., 1982). In Kawasaki disease, urinary mercury
excretion is not always elevated, whereas it is in Pink
disease.

9.5. Carcinogenicity

Inorganic mercury is generally not considered to be
carcinogenic in humans (Kazantzis, 1981; Kazantzis &
Lilly, 1986). However, recent observations have shown an
excess risk of glioblastoma among Swedish dentists and
dental nurses (Ahlbom et al., 1986). Based on the Swedish
Cancer Environment Registry covering the years 1961-1979,
a standardized morbidity ratio of 2.1 was observed (with
95% confidence limits 1.3-3.4). The authors concluded that
the most probable origin is some occupational factor com-
mon to dentists and dental nurses, e.g., amalgam, chloro-
form, or radiography.

Cragle et al. (1984) published results of a mortality
study of men exposed to elemental mercury. It was a retro-
spective cohort study of 5663 workers selected from about
14 000 workers in the Y-12 plant in Oak Ridge, USA, orig-
inally working on the Manhattan Project but later in a
programme to produce large quantities of enriched lithium.
Elemental mercury was used in the lithium isotope separ-
ation process. Mercury urinalysis testing started in mid-
1953. Urine concentrations were not reported, but air
mercury levels in 50-80% of the samples taken during the
early 1950s were above 100 $\mu g/m^3$. The workers studied
were divided into three groups: two exposed groups and one
non-exposed group. It is not possible to evaluate the
design as no valid exposure and selection data were pre-
sented. In all three groups, elevated SMRs (2.3, 1.2, 2.1)
for tumours of the central nervous system were found.
However, a statistically significant increase was reported
only for the group consisting of 3260 non-mercury workers.

9.6. Mutagenicity and related end-points

WHO (1976) did not report any studies showing that in-
organic mercury was genotoxic to humans. However, relevant
data have since been reported. Popescu et al. (1979) com-
pared four men exposed to elemental mercury vapour with a
control group and found an increased prevalence of chromo-
somal aberrations. Verschaeve et al. (1976) and Verschaeve
& Susanne (1979) showed an increase in aneuploidy after
exposure to very low concentrations of metallic mercury
vapour, but this could not be repeated in a later study
(Verschaeve et al., 1979). Similarly, Mabille et al.
(1984) did not find an increase of structural chromosomal
aberrations in peripheral blood lymphocytes of workers
exposed to metallic mercury vapour.

9.7. Dental amalgam and general health

During recent years there has been intense debate in some countries (e.g., Sweden and USA) on the possible health hazards of dental amalgams (Ziff, 1984; Penzer, 1986; SOS, 1987; Berglund, 1989). Those who claim that mercury from amalgam may cause severe health hazards refer to information on the release of mercury from amalgam and subsequent uptake into the body due to inhalation and swallowing of mercury. They also claim that a large number of people suffer from a variety of complaints and that their symptoms are caused by mercury. Those who deny a causal relation between dental amalgams and health effects point out that amalgam has been used for many years with no proven health effects. Furthermore, the uptake of mercury from amalgam is considerably less than has been associated with effects after occupational exposure to mercury (Fan, 1987).

There are many people with sometimes clearly incapacitating complaints who believe that these are caused by dental amalgam. Reports describing different types of symptoms or other effects (Hansson, 1986; Johansson & Lindh, 1987; Siblerud, 1988) do not allow any conclusions to be reached concerning their cause. This was also the opinion of a Swedish Task Group (SOS, 1987). The symptomatic picture is highly diverse and characterized by a variety of different symptoms. Some studies reported that patients improved after their amalgam fillings were replaced by another dental filling material. However, these reports have not been controlled for potential placebo effects.

Recently results from one epidemiological study have been reported by Ahlqwist et al. (1988). The data collection was carried out during 1980-1981. The majority of participants (85%) consisted of individuals who had already in 1968-69 participated in a longitudinal descriptive study of different diseases among women in the city

of Gothenburg, Sweden. The remainder were included to expand the age strata and obtain a sample representative of women of the same age in the general population. Altogether 1024 women (aged 38-72 years) participated in the study, which covered a dental examination with an orthopantomogram and a medical examination including a standardized self-administered questionnaire regarding different symptoms or complaints. The dental and medical examinations were made by different people and without mentioning possible relations between amalgam and health risks. No positive correlations were found between number of amalgam fillings and number of symptoms or between number of amalgam fillings and prevalence of specified single symptoms or complaints. On the contrary, there were several age-matched significant correlations in the opposite direction. Some of these correlations (abdominal pain, poor appetite) disappeared when adjustment was made for number of teeth. Risk ratios (including 95% confidence limits) for women with 20 fillings or more compared to

women with 0-4 fillings are given in Table 5. The authors
concluded that their results do not support a correlation
between number of surfaces with amalgam fillings and vari-
ous symptoms studied on the population level. They do not
exclude the possibility of a connection between amalgam
fillings and special symptoms and complaints on the indi-
vidual level, but, if such a connection exists, it has a
low prevalence among the general population.

Table 5. Risk ratio for a specific symptom or
complaint for 460 women with 20 or more fillings
compared to 193 women with 0-4 fillings[a]

| Symptom or complaint | Risk ratio analysis | |
	Risk ratio	95% confidence limits for risk ratio
Dizziness	0.70	0.46-1.07
Eye complaints	1.01	0.64-1.57
Hearing defects	0.66	0.41-1.07
Headache	1.22	0.83-1.80
General fatigue	0.79	0.55-1.15
Sleep disturbances	1.38	0.94-2.03
Nervous symptoms	0.80	0.52-1.25
Sweating	0.86	0.57-1.32
Breathlessness	0.65	0.41-1.03
Chest pain	0.62	0.39-0.99
Cough	0.71	0.47-1.08
Irritability	0.68	0.45-1.02
Over-exertion	0.60	0.38-0.96
Reduced mental concentration capacity	0.74	0.47-1.18
Restlessness	0.70	0.45-1.09
Depressive symptoms	0.74	0.50-1.07
Readiness to crying	0.72	0.46-1.11
Reduced ability to relax	1.15	0.79-1.69
Abdominal pain	0.64	0.42-0.98

Table 5 (contd.)

| Symptom or complaint | Risk ratio analysis | |
	Risk ratio	95% confidence limits for risk ratio
Indisposition	1.00	0.57-1.76
Diarrhoea	0.62	0.32-1.18
Constipation	0.82	0.50-1.37
Poor appetite	0.33	0.16-0.68
Loss of weight	0.27	0.10-0.70
Overweight	0.76	0.52-1.12
Sensitivity to cold	0.78	0.50-1.21
Micturation disturbances	0.66	0.30-1.43
Joint complaints	0.97	0.66-1.43
Back complaints	0.74	0.51-1.07

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Leg complaints                 0.74      0.51-1.09
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[a] The analysis was confined to dentulous women. Age
  was taken into consideration by means of the
  Mantel-Haenszel procedure. Modified from Ahlqwist
  et al. (1988).

    Lavstedt & Sundberg (1989) investigated possible
associations between dental amalgam and a range of symp-
toms by re-examining certain dental, medical, and socio-
logical data originally collected from 1204 subjects in
1970 (i.e. prior to the present debate on dental amalgam).
Standardization was made for various confounding factors,
such as gender, social group, and smoking habits.   There
was no statistically significant increase in the percent-
age of individuals with symptoms in groups with increased
numbers of amalgam fillings after controlling for con-
founding factors. The authors pointed out that the study
did not exclude a causal association on the individual
level. One strength of the study was that practically all
of the examinations were carried out by one single
investigator.

9.8. Reproduction, embryotoxicity, and teratogenicity

9.8.1. Occupational exposure

9.8.1.1 In males

    McFarland & Reigel (1978) reported medical findings in
nine men exposed accidentally for less than 8 h when more
than 10 ml of mercury was instantly vapourized at a high
temperature. Air mercury concentrations were estimated to
be 44.3 mg/m^3.   Even if these theoretical estimates are
very uncertain, the exposure must have been extremely
high. Six of the cases developed symptoms of acute
poisoning.   During a follow-up lasting several years they

also showed signs of chronic poisoning. A loss of libido,
which persisted for at least several years, was reported
in all six cases.

    Lauwerys et al. (1985) compared the fertility of 103
male workers, exposed to elemental mercury vapour in a
zinc-mercury amalgam factory, a chloralkali plant, and in
plants manufacturing electrical equipment, with 101 well-
matched controls. The exposed group had an average blood
mercury level of 14.6 µg/litre (SD 11.6 µg/litre) and an
average urine mercury concentration of 52.4 µg/g   creati-
nine (SD 46.7 µg/g).   In the exposed group, 59 children
were born compared to 65.8 expected (as calculated from
data in the control group). However, the difference was
not statistically significant.

    In a study carried out at a US Department of Energy
plant that used very large quantities of elemental mercury
from 1953 to 1963, reproductive outcomes were studied

among 247 male workers exposed to metallic mercury vapour (Alcser et al., 1989). As controls, 255 plant workers whose job did not require exposure to elemental mercury were used. No associations were demonstrated between mercury exposure and decreased fertility, increased rates of major malformations among the offspring, or serious childhood disease. There was an association between exposure and miscarriage, which disappeared however after controlling for the number of previous miscarriages before exposure began. The 95% adjusted confidence limits were 0.97-1.18. The authors pointed out certain problems with the study. The most serious methodological weakness in the evaluation was the necessity for subject recall of events that occurred 20 to 50 years previously. Another problem, which was not considered, was possible exposure to other toxic substances in the control group. The higher frequency of miscarriages among the exposed group prior to the exposure period could not be explained.

9.8.1.2 In females

There have been reports of increased menstrual disturbances in women exposed industrially or in dentistry to elemental mercury vapour. A study by De Rosis et al. (1985) examined a group of 106 women exposed to low levels of mercury (average values not exceeding 10 $\mu g/m^3$) and a control group of 241 unexposed women in another factory with similar working conditions. The percentage of women having normal menstrual cycles at the start of employment was very similar in both groups of women. During their period of employment more women in the exposed group noticed changes in the menstrual cycle than women in the control group. The age-standardized ratio of abnormal cycle frequency in exposed women to that in the control group was 1.4. The information was obtained by means of interviews, but these were not carried out on a blind

basis. Therefore, according to the authors, the results neither prove nor exclude the possibility that occupational exposure to this concentration of mercury has a negative effect on the female reproductive system.

There have been reports which suggest that inorganic mercury compounds cause spontaneous abortion. Goncharuk (1977) reported that during a 4-year period 17% of 168 exposed workers in a mercury smelting plant had experienced spontaneous abortion (average exposure, 80 μg mercury per m^3), compared with 5% among 178 controls. Toxaemia during pregnancy was reported in 35% of the exposed and 2% of the unexposed workers. Gordon (1981) reported a slightly elevated incidence of spontaneous abortions among dentists. The results can not be interpreted with certainty, however, due to a non-response rate of almost 50%. The study of De Rosis et al. (1985), referred to earlier in this section, revealed no difference in the age-standardized rate of spontaneous abortion between mercury-exposed and unexposed female workers. Two other studies

of female dental staff also reported no increased abortion
rate when compared with age-standardized controls. In one
of the studies (Heidam, 1984), the upper 95% confidence
limit for odds ratio was about 2. In the other study
(Brodsky et al., 1985), a comparison was made between a
"low" exposure group and a "high" exposure group. The
low exposure group comprised dental assistants preparing
less than 40 amalgam restorations per week and the high
exposure group those preparing more than 40 fillings a
week. The assumed difference in exposure between the
groups was not validated by measurements.

Two studies, one from Poland and one from Sweden, both
dealing with spontaneous abortions and malformations, are
of particular interest. The Polish study (Sikorski et al.,
1987) revealed a high frequency of malformations among
dental staff. Of 117 pregnancies in the mercury-exposed
group, 28 pregnancies in 19 women led to reproductive
failure, such as spontaneous abortion (19 cases, 16.2%),
stillbirth (3 cases, 2.6%), congenital malformations (5
cases of spina bifida, 5.1%; one case of intra-atrial
defect). This contrasts, in non-exposed controls, with
seven cases of adverse pregnancy outcome (11.1%) in five
women out of a total of 63 pregnancies (30 women). There
were no malformations among the controls (R. Sikorski,
personal communication to the IPCS). The age distribution
of exposed and control women and the number of pregnancies
before exposure or effect were not reported, which makes
it difficult to interpret the data. For most countries the
average rate of spina bifida is 5-10 (or less) per 10 000
births (International Clearing-house for Birth Defects
Monitoring System, 1985) over a wide age span. Sikorski et
al. (1987) reported a correlation between mercury levels
in hair and reproductive failure in the exposed group. The
meaning of this correlation is difficult to interpret, as

hair is not a good indicator of exposure to metallic mer-
cury vapour, due to several factors, including the possi-
bility of external contamination (section 6.5.2). There is
reason to believe, however, that the exposure was higher
in the group with higher hair mercury levels (R. Sikorski,
personal communication to the IPCS). Only 13.6% of the
women studied used automatic amalgamators. The remaining
86.4% prepared the amalgam in an open mortar and almost
never in separate rooms.

The Swedish study was reported by Ericson & Källén
(1989), linking data from the Swedish National registers
for birth records, malformations, and occupation.
Altogether, 8157 children born to dentists (1360), dental
nurses (6340), and dental technicians (457) were compared
with the total number of births in Sweden during the
observation period (1976, 1982-1986). The analysis took
into consideration different confounding variables, such
as the age of the mother and number of children. The
study also examined the occurrence of stillbirths and
spontaneous and induced abortions treated in hospitals.

There was no tendency towards an elevated rate of malformation, abortion, or stillbirth. The study did not verify the high risk of spina bifida described in the Polish study (Sikorski et al., 1987). In spite of the large study group, the upper 95% confidence limit for the risk ratio of spina bifida was high (2.1), and the upper confidence limit of the absolute risk was about 1 per 1000 births. Therefore, the study is not a strong argument against an effect. In addition, a sample of 3991 pregnancies from the 1960s (among them there were 13 dentists, 65 dental assistants, and 6 dental technicians) was studied but no effects on spontaneous abortion rate or malformation was seen. The authors point out, however, that the only malformed infant observed had anencephaly and that both parents worked as dental technicians.

Among dental nurses, there was a significant excess of children with a birth weight of 2 to 2.5 kg. In total there were 274 children weighing less than 2.5 kg (against an expected number of 233), which gives a risk ratio for low birth weight of 1.2 (with a 95% confidence interval of 1.0-1.3). No similar excess in low birth weight was seen among dentists or dental technicians. Possible confounding socioeconomic factors, e.g., smoking, were not studied, but the authors suggested that these findings could be explained by differences in socioeconomic status.

During recent years much interest has focused on subclinical developmental changes in children exposed in utero or in early childhood to methylmercury and lead. No similar studies have been reported for inorganic mercury.

10. EVALUATION OF HUMAN HEALTH RISKS

Mercury exists in different forms, including elemental mercury, inorganic mercury and organic mercury compounds. They have some properties in common but differ in metabolism and toxicity. Biotransformation takes place in the body, particularly the transformation of metallic mercury vapour to mercuric compounds, which means that some of the effects of inorganic mercury could also be expected after exposure to metallic mercury vapour. There are, however, no empirical data showing whether or not inorganic mercury formed due to a biotransformation has similar toxicity and metabolism to that of inorganic mercury accumulated in the body as a result of exposure to inorganic mercury itself. It would be prudent to consider, until more information is available, that, with the exception of acute renal tubular cell damage, the two forms of inorganic mercury have similar toxicity.

10.1. Exposure levels and routes

10.1.1. Mercury vapour

Human long-term exposure to mercury vapour is primarily encountered in an occupational setting and in cases

where the metal has been handled inappropriately in the home. Continual low-level exposure to mercury vapour occurs in the mouth in the presence of dental amalgam fillings. The amount of mercury vapour released intra-orally depends on the number, surface area, and mechanical loading of the amalgam restorations. Atmospheric levels of mercury found in the workplace, e.g., chloralkali plants, are usually below 50 µg/m^3. Levels above 50 µg/m^3 and even exceeding 100 µg/m^3 can be found in work environ-ments where good industrial hygiene has not been practiced or in home operations, in which the highest levels would be expected. Values for air concentration (in µg/m^3) are approximately the same as those for urine mercury concen-tration (expressed in µg/g creatinine). The use of urinary mercury excretion makes it possible to compare intake from the working atmosphere and release from dental amalgam.

Occupational exposure to mercury vapour in dentistry has been well established, reported exposure levels being 4-30 µg/m^3, on average, with up to 150-170 µg/m^3 in some clinics. The values for mean intraoral mercury vapour concentration derived from dental amalgam have been reported to be in the range of 3 to 29 µg/m^3.

Approximately 80% of inhaled mercury vapour is absorbed from the lungs, while uptake of mercury vapour via the skin is about 1% of uptake by inhalation. No data are available on the possible oral mucosal absorption of mercury vapour. Mercury vapour can cross the plancental barrier, thus exposing the developing fetus.

10.1.2. Inorganic mercury compounds

The major source of high exposure to humans from mer-curic compounds involves medicaments, both traditional and alternative, and skin-lightening creams and soaps. There is some evidence from occupational settings where chlorine is used that a part of the mercury vapour can be trans-formed in the atmosphere and absorbed as an aerosol of mercuric mercury. Mercuric mercury is to a great extent deposited in the placenta, where it causes damage that may lead to adverse effects on the fetus.

Mercurous mercury, in the form of calomel, has for long been used in therapeutics. The mercury content in the brain of two daily users of calomel, ingesting 240 mg mercurous chloride per day, was 4-106 mg/kg brain, indi-cating that elemental mercury is formed from mercurous chloride following ingestion.

10.2. Toxic effects

10.2.1. Mercury vapour

Over-exposure to mercury vapour gives rise to neuro-logical effects with initially a fine high-frequency

intention tremor and neurobehavioural impairment. Periph-
eral nerve involvement has also been observed. Proteinuria
and lysosomal enzymes in the urine of exposed workers
indicate an effect on the kidney of chloralkali workers;
the presence of mercuric mercury may have contributed to
this effect. The nephrotic syndrome has been reported
among chloralkali workers. Pink disease, skin allergy, and
mucocutaneous lymph node syndrome (Kawasaki disease) in
children, have also been observed after exposure to mer-
cury vapour.

Hypersensitivity skin reactions have been described
after exposure to metallic mercury vapour from mercury
amalgam materials. No data supporting carcinogenic effects
of mercury vapour have been reported. There has been a
report of excess risk of glioblastoma observed in Swedish
dental personnel. At this stage, however, it has not been
possible to associate this excess risk with any specific
group of dental materials. The standard of published
epidemiological studies is such that it remains an open
question whether mercury vapour can adversely affect the
menstrual cycle or fetal development in the absence of the
well-known signs of mercury intoxication.

10.2.2. Inorganic mercury compounds

Information on pulmonary deposition and absorption of
mercuric mercury aerosols is lacking. However, it is
likely that significant absorption takes place directly
from the lung and probably from the gastrointestinal tract
after mucociliary clearance from the lung.

Most adverse effects of mercuric compounds in humans
have been reported after oral ingestion or skin absorp-
tion. However, only limited information is available as
far as dose-effect relationships are concerned. From
animal experiments it is possible to identify the critical
lowest effect levels that are likely to result in protein-
uria in humans after chronic exposure. Proteinuria in
humans is believed to be produced through the formation of
mercuric-mercury-induced autoimmune glomerulonephritis.
The production and deposition of IgG antibodies to glomer-
ular basement membrane can be considered the first step in
the formation of this glomerulonephritis. No data on
possible carcinogenic effects of mercuric mercury have
been reported.

10.3. Dose-response relationships

10.3.1. Mercury vapour

The risk assessment of exposure to mercury vapour is
hindered by the heterogeneity of published data, problems
with the estimation of exposure (e.g., lack of speciation
and methodological uncertainties), uncertainty concerning
the reliability of subjective symptoms, and the selection
of control groups for comparison with low exposure groups.

Nevertheless the data presented in section 9 allow a broad characterization to be made.

a) When exposure is above 80 µg/m^3, corresponding to a urine mercury level of 100 µg/g creatinine (section 6.5.2), the probability of developing the classical neurological signs of mercury intoxication (tremor, erethism) and proteinuria is high.

b) Exposure in the range of 25 to 80 µg/m^3, corresponding to a level of 30 to 100 µg mercury/g creatinine, increases the incidence of certain less severe toxic effects that do not lead to overt clinical impairment. These subtle effects are defects in psychomotor performance, objectively detectable tremor, and evidence of impaired nerve conduction velocity, which are present only in particularly sensitive individuals. The occurrence of several subjective symptoms, such as fatigue, irritability, and loss of appetite, is also increased. In a few studies, tremor, recorded electrophysiologically, has been observed at low urine concentrations (down to 25-35 µg/g creatinine). Other studies did not show such an effect. Although the incidence of some signs was increased in this exposure range, most studies did not find a dose-response relationship. Some of the exposed people develop proteinuria (proteins of low relative molecular mass and microalbuminuria). The available studies are generally of small size and low statistical power.

c) Appropriate epidemiological data covering exposure levels corresponding to less than 30-50 µg mercury per g creatinine are not available. Since a specific no-observed-effect level cannot be established and if larger populations are exposed to low concentrations of mercury, it cannot be excluded that mild adverse effects may occur in certain sensitive individuals.

Some studies have found miscarriages and abortions after occupational exposure to mercury, but other studies did not confirm these effects. The WHO Study Group in 1980 stated: "The exposure of women of child-bearing age to mercury vapour should be as low as possible. The Group was not in a position to recommend a specific value" (WHO, 1980). This statement is still prudent and will remain so until new data become available.

10.3.2. Inorganic mercury compounds

The risk assessment of exposure to inorganic mercury compounds is hindered by a lack of adequate human data dealing with the relationship between dose and effects/responses. For this reason, more human research is needed in order to arrive at the goal of a human risk evaluation of inorganic mercuric mercury compounds at low levels.

The intake of gram doses of mercuric chloride causes severe to lethal renal tubular damage and necrosis of the gastrointestinal mucous membrane. At lower dose levels, less pronounced tubular damage occurs, reflected in amino-aciduria, increased diuresis, and loss of renal enzymes in the urine.

A special problem in the risk assessment of mercury is the fact that mercury can give rise to allergic and immu-notoxic reactions, which are partly genetically regulated. There may well be a small fraction of the population that is particularly sensitive, as has been observed in animal studies. A consequence of an immunological etiology is that it is not scientifically possible to set a level for mercury, e.g., in blood or urine, below which mercury-related symptoms will not occur in individual cases, since dose-response studies for groups of immunologically sensi-tive individuals are not yet available.

Based upon the evaluation in animals, the most sensi-tive adverse effect for inorganic mercury risk assessment is the formation of mercuric-mercury-induced auto-immune glomerulonephritis, the first step being the production and deposition of IgG antibodies to the glomerular base-ment membrane. The Brown Norway rat is a good test species for the study of mercuric-mercury-induced auto-immune glomerulonephritis (although this effect has also been observed in rabbits), and it is the best animal model for the study of mercury-induced kidney damage at present. The

group of studies presented in Table 4 (section 8.2.2.6) was selected for consideration of mercuric mercury risk assessment. A no-observed-adverse-effect level (NOAEL) could not be determined from these animal studies. The lowest-observed-adverse-effect level (LOAEL) was found in the subcutaneous exposure study by Druet et al. (1978). In this study, subcutaneous doses of mercuric chloride (0.05 mg/kg body weight three times per week) were administered for 12 weeks and resulted in antibodies being bound to the glomerular basement membrane of the rat kidney.

Using this animal LOAEL (0.05 mg/kg), equivalent human oral and inhalation LOAEL values for kidney effects can be determined as follows:

Average daily subcutaneous dose:

$$= \frac{(0.05 \text{ mg/kg}) \times 3 \text{ days} \times 0.739}{7 \text{ days}} = 0.0158 \text{ mg/kg per day}$$

where: 0.05 mg/kg = dose of $HgCl_2$ injected subcutaneously into rats
3 days = number of days per week that doses were administered
7 days = number of days per week
0.739 = fraction of $HgCl_2$ that is Hg^{2+} ion.

Although the calculated values have been rounded, the un-rounded values were always used in subsequent calculations.

Human oral exposure equivalent determination:

$$= \frac{(0.0158 \text{ mg/kg per day}) \times 70 \text{ kg} \times 100\%}{7\%} = 15.8 \text{ mg/day}$$

where: 0.0158 mg/kg per day = average daily subcutaneous dose of Hg^{2+}
70 kg = assumed body weight of an adult human
100% = assumed percentage of Hg^{2+} absorbed from the subcutaneous route of exposure
7% = assumed percentage of Hg^{2+} absorbed from the oral route of exposure

Human inhalation exposure equivalent determination:

a) For 24-h general population exposure:

$$\frac{(0.0158 \text{ mg/kg per day}) \times 70 \text{ kg} \times 100\%}{(20 \text{ m}^3/\text{day}) \times 80\%} = 0.069 \text{ mg/m}^3$$

where: 0.0158 mg/kg per day = average daily subcutaneous dose of Hg^{2+}
70 kg = assumed body weight of an adult

20 m^3/day = assumed volume of air inhaled during a 24-h period
100% = assumed percentage of Hg^{2+} absorbed from subcutaneous route of exposure
80% = assumed percentage of Hg^0 absorbed from the lung.

b) For 8-h work-day exposure:

$$\frac{(0.0158 \text{ mg/kg per day}) \times 70 \text{ kg} \times 100\%}{(10 \text{ m}^3/\text{day}) \times 80\%} = 0.139 \text{ mg/m}^3$$

where: 0.0158 mg/kg per day = average daily subcutaneous dose of Hg^{2+}
70 kg = assumed body weight of an adult
10 m^3 = assumed volume of air inhaled during a work-day
100% = assumed percentage of Hg^{2+} absorbed from subcutaneous route of exposure
80% = assumed percentage of Hg^0 absorbed from the lung.

These inhalation LOAEL values calculated for kidney effects are well within the range of mercury vapour exposures in humans where neurological and renal effects have been observed.

11. RECOMMENDATIONS FOR FURTHER RESEARCH

Further research is required in the following areas:

1. Determination of the exposure to different chemical forms of mercury at low levels of exposure, including the development of microtechniques for speciation of small quantities of mercury in biological materials and of analytical quality assurance techniques.

2. The pharmacokinetics of mercury release from amalgam restorations in relation to time, diet, technical and physiological conditions, and the development of tests for identifying specially sensitive individuals (e.g., local mucosa reactions, intra-oral electrochemical measurements, immunotoxicity).

3. The use of mercury compounds in pharmaceuticals and cosmetics.

4. The binding, biotransformation, and transport of different forms of mercury, both in animals and humans, including interactions with selenium.

5. The transplacental transport of mercury and specific distribution in fetal organs, fetotoxic effects, and developmental effects with emphasis on neurobehavioural effects.

6. Research on the neurobehavioural effects of mercury in the occupationally exposed population (dentists, etc.).

7. The epidemiology of the role of mercury in inducing glomerulonephritis in the general population.

8. The prevalence of immunological effects and hypersensitivity in low-dose exposure to mercury with or without subjective symptoms.

9. A case-control study of brain tumours, in particular glioblastoma, and exposure to mercury.

Measures to decrease the exposure of the general population to mercury-containing pharmaceuticals and cosmetics should be promoted.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The human health risks of inorganic mercury compounds were previously evaluated in Environmental Health Criteria 1: Mercury (WHO, 1976). More recent evaluations by the International Programme on Chemical Safety (IPCS) have dealt mainly with the health risks of methylmercury exposure (WHO, 1990). A WHO review of the occupational health risks of inorganic mercury (WHO, 1980) and an IPCS review of the environmental aspects of mercury (WHO, 1989)

have been published. The recommended health-based occupational exposure limit for metallic mercury vapour (WHO, 1980) is 25 µg mercury/m^3 air (TWA, long-term exposure) and 500 µg mercury/m^3 air (peaks, short-term exposure). The equivalent value for long-term exposure to inorganic mercury compounds is 50 µg mercury/m^3 air (TWA) (WHO, 1980). A maximum individual urine mercury concentration of 50 µg/g creatinine has also been recommended (WHO, 1980).

Regulatory standards established by national bodies in various countries and in the European Community are summarized in the data profile of the International Register of Potentially Toxic Chemicals (IRPTC, 1987).