# IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

## Environmental Health Criteria 101

# Methylmercury

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**Environmental Health Criteria 101**

# METHYLMERCURY

Published under the joint sponsorship of
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and the World Health Organization

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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, 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 - 7985850).

# ENVIRONMENTAL HEALTH CRITERIA FOR METHYLMERCURY

A WHO Task Group on Environmental Health Criteria for Methylmercury met in Bologna, Italy, at the Provincia from 5 to 9 June 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 Provincial Government. Dr C. Maltoni, Director of the Institute, welcomed the participants on behalf of the host institution and the local governments, and Dr M. Ancora, C.I.S.I., spoke on behalf of the Ministry of the Environment. Dr M. Mercier, Manager, IPCS, addressed the meeting on behalf of the three cooperating organizations of the IPCS (ILO/UNEP/WHO), reviewing the accomplishments of the Programme over the last few years.

The Task Group made minor revisions to the draft document and made an evaluation of the human health risks from exposure to methylmercury.

The efforts of DR T. CLARKSON, University of Rochester, Rochester, New York, USA, who prepared the first two drafts of this document, and all others who helped in its preparation and finalization are gratefully acknowledged. Dr G. Becking and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the overall scientific content and technical editing, respectively.

* * *

Financial support for the meeting was provided by the Ministry of the Environment of Italy, and the Centro Italiano Studi e Indagini and the Institute of Oncology, Bologna, contributed to the organization and provision of meeting facilities.

# 1. SUMMARY AND CONCLUSIONS

This monograph focuses on the risks to human health from compounds of monomethylmercury and examines the data that have become available since the publication of Environmental Health Criteria 1: Mercury (WHO, 1976b). The environmental effects of mercury are discussed in Environmental Health Criteria 86: Mercury - Environmental Aspects (WHO, 1989a).

## 1.1 Identity, Physical and Chemical Properties, Analytical Methods

The solubility of methylmercury compounds in water varies greatly and depends on the nature of the anion. Most are soluble in water but much less soluble in non-polar solvents. They generally have appreciable vapour pressures at room temperature. Mercurials, including alkylmercurials, exhibit high affinities for sulfhydryl groups.

Blood samples for analysis should be taken by venipuncture, avoiding devices using mercury-containing preservatives. Current methods are capable of measuring mercury in 1- to 5-ml samples of whole blood, even in the case of non-exposed individuals. Hair is useful in assessing exposure to methylmercury in the diet and may be sampled as single or bunched strands. The single-strand procedure requires both sensitive analytical methods and the determination of the growth phase of the hair.

The method of choice for determining total mercury in environmental and biological samples is flameless atomic absorption spectroscopy (detection limits, 0.5-4.0 ng/g). Neutron activation analysis serves as a sensitive reference method. Gas chromatography is used to determine methylmercury directly (detection limit, 1.0 ng/g sample).

## 1.2 Sources of Human and Environmental Exposure

Environmental methylmercury arises largely, if not solely, from the methylation of inorganic mercury. The major source of atmospheric mercury is the natural

degassing of the earth's crust, amounting to 2700-6000 tonnes per year. Deposition of atmospheric mercury, leaching from rocks, and anthropogenic sources all add to the mercury burden in bodies of water, but the exact contribution of each source is indeterminable.

About 10 000 tonnes of mercury per year are mined, subject to considerable year-to-year variation. Other important man-made sources are fossil fuels combustion, smelting of sulfide ores, production of cement, and refuse incineration. The total man-made global release of mercury to the atmosphere is approximately 2000-3000 tonnes per year, i.e., less than the natural emissions. Man-made emissions pose the greatest risk when they are released in confined areas.

Mercury continues to be used in the production of caustic soda and chlorine, and it is widely used in the electrical industry for lamps, controls, rectifiers, batteries and switches, as well as in the dental profession. Environmental losses can also occur from its continued use in antifouling and mildew-proofing paints, in seed dressings, and in the extraction of gold.

## 1.3 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 it is likely that deposition will occur within a short distance.

The change in speciation of mercury from inorganic to methylated forms is the first step in the aquatic bioaccumulation process. Methylation can occur non-enzymically or through microbial action. Once methylmercury is released, it enters the food chain by rapid diffusion and tight binding to proteins. As a result of food-chain biomagnification, highest levels are found in the tissues of such predatory species as freshwater trout, pike, walleye, bass and ocean tuna, swordfish, and shark. The bioconcentration factor, i.e., the ratio of the concentration of

methylmercury in fish tissue to that in water, is usually between 10 000 and 100 000. Levels of selenium in the water may affect the availability of mercury for uptake into aquatic biota. Reports from Sweden and Canada suggest that methylmercury concentrations in fish may increase following the construction of artificial water reservoirs.

## 1.4 Environmental Levels and Human Exposure

The general population is primarily exposed to methylmercury through the diet. However, air and water, depending upon the level of contamination, can contribute significantly to the daily intake of total mercury. In most foodstuffs, mercury is largely in the inorganic form and below the limit of detection (20 μg mercury/kg fresh weight). However, fish and fish products are the dominant source of methylmercury in the diet, and levels greater than 1200 μg/kg have been found in the edible portions of shark, swordfish, and Mediterranean tuna. Similar levels have been found in pike, walleye, and bass taken from polluted fresh waters.

It has been estimated that humans have a daily intake of about 2.4 μg methylmercury from all sources, and a daily uptake of approximately 2.3 μg. The total daily intake of *all* forms of mercury from all sources has been estimated to be 6.7 μg, with an added burden of 3.8 to 21 μg of mercury vapour from dental amalgams, if present. The level of mercury in fish, even for humans consuming only small amounts (10-20 g of fish/day), can markedly affect the intake of methylmercury. The consumption of 200 g of fish containing 500 μg mercury/kg will result in the intake of 100 μg mercury (predominantly methylmercury). This amount is one-half of the recommended provisional tolerable weekly intake (WHO 1989b).

## 1.5 Kinetics and Metabolism

Methylmercury in the human diet is almost completely absorbed into the bloodstream and distributed to all tissues within about 4 days. However, maximum levels in the brain are only reached after 5-6 days. In humans, blood to hair ratios are about 1:250, with appreciable individual

variation. Similarly, large individual differences are seen in cord to maternal blood mercury ratios, the levels generally being higher in cord blood. Species differences exist in the distribution of methylmercury between red blood cells and plasma (about 20:1 in humans, monkeys, and guinea-pigs, 7:1 in mice, and >100:1 in rats).

Methylmercury is converted to inorganic mercury in experimental animals and humans. The duration of the exposure and the interval after its cessation, determine the fraction of total mercury present in tissues in the $Hg^{++}$ form. In humans, after high oral intakes of methylmercury for 2 months, the following values were reported (percentage of total mercury in tissues as inorganic mercury): whole blood, 7%; plasma, 22%; breast milk, 39%; urine, 73%; liver, 16-40%.

The rate of excretion of mercury in both laboratory animals and humans is directly proportional to the simultaneous body burden and can be described by a single-compartment model with a biological half-time, in fish-eating humans, of 39-70 days (average approximately 50 days). Lactating females have significantly shorter half-times for mercury excretion than non-lactating ones.

Mercury half-times in hair closely follow those in blood but with wider variation (35-100 days, average 65 days). Suckling mice are incapable of excreting methylmercury, but they abruptly change to the adult rate of excretion at the end of the suckling period.

In the case of continuous exposure, a single-compartment model with a 70-day half-time predicts that the whole-body steady state (where intake equals excretion) will be attained within approximately one year and that the maximum amount accumulated will be 100 times the average daily intake. The validity of the single-compartment model is supported by the reasonable agreement between predicted and observed blood concentrations of methylmercury in single-dose tracer studies, single-dose fish intake experiments, and studies involving the extended controlled intake of methylmercury from fish. It is also supported by results from the longitudinal hair analysis of individuals with very high intakes of methylmercury.

Mean reference values for total mercury in commonly used indicator media are: whole blood, 8 μg/litre; hair, 2 μg/g; urine, 4 μg/litre, and placenta, 10 μg/kg wet weight. Long-term fish consumption is the major determinant of methylmercury and, usually, total mercury levels in blood. For example, in communities in which there is a long-term daily consumption of 200 μg mercury/day from fish, blood mercury levels are approximately 200 μg/litre and corresponding hair levels about 250 times higher (50 μg/g hair).

## 1.6 Effects on Experimental Animals and *In Vitro* Systems

In every animal species studied, the nervous system is a target of methylmercury, fetuses appearing to be at higher risk than adults. Concerning effects on the nervous system, animal studies reported since 1976 provide further support to the mechanistic models used to evaluate the available data in humans (summarized in section 1.7).

Methylmercury is fetoxic in mice (single dose of 2.5-7.5 mg/kg); teratogenic in rats, and adversely affects the behaviour of monkey offspring (mercury doses of 50-70 μg/kg per day before and during pregnancy). It also affects spermatogenesis in mice (1 mg mercury/kg as methylmercury).

## 1.7 Effects on Man - Mechanism of Action

The effects of methylmercury on adults differ both qualitatively and quantitatively from the effects seen after prenatal or, possibly, early postnatal exposures. Thus, effects on the mature human being will be considered separately from the effects on developing tissues.

The clinical and epidemiological evidence indicates that prenatal life is more sensitive to the toxic effects of methylmercury than is adult life. The inhibition of protein synthesis is one of the earliest detectable biochemical effects in the adult brain, though the sequence of events leading to overt damage is not yet understood. Methylmercury can also react directly with important receptors in the nervous system, as shown by its effect on acetylcholine receptors in the peripheral nerves. In the case of prenatal exposure, the effects of methylmercury

seem to be quite different and of a much more general basic nature. It affects normal neuronal development, leading to altered brain architecture, heterotopic cells, and decreased brain size. Methylmercury may also be exerting an effect, perhaps through inhibition of the microtubular system, on cell division during critical stages in the formation of the central nervous system.

Since 1976, a wealth of data has been reported on dose-effect and dose-response relationships in humans. It has been derived from in-depth studies on populations exposed to methylmercury through mass poisonings or through the consumption of fish containing varying levels of methylmercury. Again, prenatal and adult data will be considered separately in view of the differences, both qualitative and quantitative, in effects and dose-response relationships.

In adults, the reported relationships between response and body burden (hair or blood mercury concentrations) are essentially the same as those reported in Environmental Health Criteria 1: Mercury (WHO, 1976b). No adverse effects have been detected with long-term daily methylmercury intakes of 3-7 μg/kg body weight (hair mercury concentrations of approximately 50-125 μg/g). Pregnant women may suffer effects at lower methylmercury exposure levels than non-pregnant adults, suggesting a greater risk for pregnant women.

Severe derangement of the developing central nervous system can be caused by prenatal exposure to methylmercury. The lowest level (maximum maternal hair mercury concentration during pregnancy) at which severe effects were observed was 404 μg/g in the Iraqi outbreak and the highest no-observed-effect level for severe effects was 399 μg/g. Fish-eating populations in Canada and New Zealand have also been studied for prenatal effects, but exposure levels were far below those that caused effects in Iraq and no severe cases were seen.

Evidence of psychomotor retardation (delayed achievement of developmental milestones, a history of seizures, abnormal reflexes) was seen in the Iraqi outbreak at maternal hair levels below those associated with severe effects. The extrapolation of data suggested that one of

these effects (motor retardation) rose above the background frequency at maternal hair levels of 10-20 μg/g. The Canadian study reported that abnormal muscle tone or reflexes were positively associated with maternal hair levels in boys but not in girls (the highest maternal hair level during pregnancy was 23.9 μg/g). The New Zealand study reported evidence of developmental retardation (according to the Denver Test) in 4-year-old children at average maternal hair mercury levels during pregnancy within the range of 6-86 μg/g (the second highest value was 19.6 μg/g). The New Zealand mercury values should be multiplied by 1.5 to convert to maximum maternal hair levels in pregnancy.

## 1.8 Conclusions

The general population does not face a significant health risk from methylmercury. Certain groups with a high fish consumption may attain a blood methylmercury level (about 200 μg/litre, corresponding to 50 μg/g of hair) associated with a low (5%) risk of neurological damage to adults.

The fetus is at particular risk. Recent evidence shows that at peak maternal hair mercury levels above 70 μg/g there is a high risk (more than 30%) of neurological disorder in the offspring. A prudent interpretation of the Iraqi data implies that a 5% risk may be associated with a peak mercury level of 10-20 μg/g in maternal hair.

There is a need for epidemiological studies on children exposed *in utero* to levels of methylmercury that result in peak maternal hair mercury levels below 20 μg/g, in order to screen for those effects only detectable by available psychological and behavioural tests.

# 2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

## 2.1 Identity

The primary constituent is the element mercury (CAS registry number 7439-97-6), which has a relative atomic mass of 200.59. In the inorganic form, mercury exists in three oxidation states: $Hg^{o}$ (metallic); $Hg_2^{++}$ (mercurous); and $Hg^{++}$ (mercuric). The mercurous and mercuric states can form numerous inorganic and organic chemical compounds. The organic forms are those in which mercury is attached covalently to at least one carbon atom.

This monograph focuses on the risk to human health of the compounds of monomethylmercury. The generic term "methylmercury" is used throughout this text to represent monomethylmercury compounds. In many cases the exact identity of these compounds is not known except that the methylmercury cation, $CH_3Hg^+$, is associated either with a simple anion, like chloride, or a large molecule (e.g., a protein) with negative and positive charges.

Other physical and chemical forms of mercury are discussed in this monograph where they are relevant to the full evaluation of the risks to human health of methylmercury: for example, the atmospheric transport of elemental mercury vapour ($Hg^{o}$), its deposition and oxidation in natural waters, and the subsequent methylation of inorganic mercury ($Hg^{++}$).

## 2.2 Physical and Chemical Properties

In its elemental form, mercury at room temperature is a heavy silvery liquid. At 20 °C the specific gravity of the metal is 13.456 and the vapour pressure is 0.16 Pa (0.0012 mmHg). Thus the saturated atmosphere at 20 °C contains mercury vapour at a concentration of approximately 15 mg/$m^3$. This concentration is over 200 fold greater than the currently accepted concentrations for occupational exposure.

It is of interest that certain forms of mercury, such as the methyl and ethyl derivatives, have appreciable

vapour pressure at room temperature. Thus, the vapour pressure of methylmercuric chloride is 1.13 Pa (0.0085 mmHg) and the vapour pressure of dimethylmercury is several times greater. Mercurials differ greatly in their solubilities. Solubility in water increases in the order: mercurous chloride; elemental mercury; methylmercuric chloride; mercuric chloride. Certain species of mercury are soluble in non-polar solvents. These include elemental mercury and the halide compounds of alkylmercurials.

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

## 2.3 Conversion Factors

1 ppm = 1 mg/kg = 1 μg/g = 1 ng/mg
1 ppb = 1 μg/kg = 1 ng/g
1 μmol mercury ≡ 1 μmol methylmercury ≡ 200 μg mercury

## 2.4 Analytical Methods

### 2.4.1 *Sampling*

Many different sampling procedures are used in the measurement of mercury. Procedures for environmental sampling in air, water, soil, and aquatic and animals species are beyond the scope of this monograph. Since its purpose is to evaluate the risks to human health, only the sampling of human indicator media and tissues will be considered.

Blood samples should be taken by venipuncture, the most convenient method being the use of heparinized "Vacutainers"[a]. Some commercial containers may contain a mercury compound added as a preservative. It is wise to analyse each commercial batch for mercury before use. The sample should be refrigerated but not frozen, as it is sometimes useful to measure mercury in plasma and red

[a] Trade name of heparinized test-tube manufactured by Becton & Dickinson, USA, and used for blood sample collection.

cells separately. The analysis should be carried out as soon as possible to avoid haemolysis of the sample. If the sample has clotted or if extensive haemolysis has occurred, the sample should be homogenized before aliquots are taken for analysis. Current methods are capable of measuring mercury in 1- to 5-ml samples of whole blood even in the case of non-exposed individuals.

Urine sampling is not useful for individuals exposed to methylmercury, because little is excreted by this route. Hair samples are important in assessing exposure to methylmercury in the diet. Methylmercury in non-occupationally exposed individuals is incorporated into hair at the time the hair is formed, the methylmercury concentration in newly formed hair being proportional to its simultaneous concentration in blood. Once incorporated into the hair strand, its concentration remains unchanged. Thus, longitudinal analysis along a strand of hair provides a recapitulation of previous blood levels. Since hair grows at about 1 cm per month, recapitulation is possible over several months or years, depending on the length of the hair sample.

There are two sampling methods, single strands and bunched strands. The former requires a more sensitive method and the determination of the growth phase (anaphase and telophase) of each strand by the microscopic examination of the hair root. However, most methods require at least 1 mg hair and, preferably, about 10 mg. Thus, if the hair is measured in 1-cm lengths, it is necessary to have about 50 strands. The best sampling procedure is to locate 50 strands of the longest hair on the head, hold them in place with a haemostat, and cut them as close to the scalp as possible with surgical scissors. The strands are tied with a cotton thread before the haemostat is released to ensure that the individual strands remain in the same alignment. The tied bunch of hair may be stored in a plastic bag or envelope until it is analysed. Bunch analysis tends to underestimate peak concentrations due to the different growth rates of individual hairs and to mechanical displacement of individual strands during collection and subsequent handling (Giovanoli-Jakubczak & Berg, 1974; Cox et al., in press). Single-strand analysis can give a more precise temporal recapitulation and avoids certain artifacts found in bunched-strand analysis. Agreement

between concentrations of mercury in individual hair strands collected from the same person at the same time is within 10%. Nevertheless it is wise to collect more than one strand to guard against accidental contamination or breakage.

### 2.4.2 *Analytical procedures*

The methods summarized in Table 1 have been selected from a large number of publications. They are typical of the various methods available for analysis of total mercury and its inorganic or organic species.

All represent a considerable improvement on the original "dithizone" method. This method was widely used up to the introduction of atomic absorption in the late 1960s. Basically it involved the formation of a coloured complex with dithizone after all the mercury in the sample had been converted to $Hg^{++}$ compounds by oxidation in strong acids. After neutralization of excess oxidant with a reducing agent, usually hydroxylamine, the coloured complex was extracted into a non-polar solvent. After washing the extract, the colour intensity was measured on a spectrophotometer and the amount of mercury estimated from a standard curve. The limit of detection was of the order of 1-10 μg mercury so that large quantities of sample were required for such media as blood and hair.

The neutron activation procedure is regarded as the most accurate and sensitive procedure and is usually used as the reference method (WHO, 1976b). The "Magos" selective atomic-absorption method (Magos, 1971; Magos and Clarkson, 1972) has found wide application. It can determine both total and inorganic mercury and, by difference, organic mercury. The apparatus is inexpensive, portable, and does not require sophisticated facilities.

The gas chromatography method is usually used when there is a need to selectively measure methylmercury or other organic species. It has been widely used for the measurement of methylmercury in fish tissues. An alternative approach is the separation of methylmercury from inorganic mercury by volatilization (Zelenko & Kosta, 1973), ion exchange (May et al., 1987), or distillation (Horvat et al., 1988a), and the estimation of the separated

Table 1. Analytical methods for the determination of total inorganic and methylmercury

| Media | Speciation | Analytical Method | Detection Limit (ng mercury/g) | Comments | References |
|---|---|---|---|---|---|
| Food, tissues | total mercury | atomic absorption | 2.0 | method has many adaptations (see Peter & Strunc, 1984) | Hatch & Ott (1969) |
| Blood, urine, hair, tissues | total mercury<br>inorganic mercury | atomic absorption | 0.5 | also estimates organic mercury as difference between total and inorganic | Magos & Clarkson (1972) |
| Blood, urine, hair, tissues | total mercury<br>inorganic mercury | atomic absorption | 2.5 | automated form of the Magos Method | Farant et al. (1981) |
| Blood, urine, hair, tissues | total mercury<br>inorganic mercury | atomic absorption | 4.0 | automated form of the Magos Method | Coyle & Hartley (1981) |
| Food, tissues, biological fluids | methylmercury | gas chromatography electron-capture | 1.0 | based on the original method of Westoo (1968) | Von Burg et al. (1974)<br>Cappon & Smith (1978) |
| All media | total mercury | neutron activation | 0.1 | reference method | Kosta & Byrne (1969)<br>Byrne & Kosta (1974) |

methylmercury by non-selective methods (e.g., atomic absorption).

The estimation of total mercury in a single strand of hair by X-ray fluorescence has been described by Jaklevic et al. (1978).

Emulsion autoradiography has been widely used in experimental studies of tissue deposition of the radioisotopes of mercury. However it should be noted that photographic emulsions are also sensitive to non-radioactive inorganic forms of mercury (Rodier & Kates, 1988).

It is necessary to note that, since methylmercury is not a sample contaminant, external contamination does not interfere with methylmercury-specific methods. Greater care is required when the method is sensitive to inorganic mercury contamination (Mushak, 1987).

### 2.4.3 *Quality control and quality assurance*

The analysis of most samples of hair or blood involves very small quantities of mercury (in the ng or even sub-ng ranges). Therefore, considerable attention should be paid to procedures that will ensure accurate analytical data. The general considerations of quality control and quality assurance have been discussed at a recent WHO-sponsored conference on Biological Monitoring of Toxic Metals (Friberg, 1988). A Global Environmental Monitoring System (GEMS) programme has been described in which a new approach to interlaboratory comparisons has been successfully introduced on an international basis. Specific quality-control programmes for mercury using the GEMS approach have been described by Friberg (1983) and Lind et al. (1988a).

# 3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

## 3.1 Natural Occurrence

As the predominant, if not only, source of environmental methylmercury is the methylation of inorganic mercury, we need to examine the environmental movement of the inorganic species if we are to understand the origins of human exposure to methylmercury. Thus, this section deals largely with the environmental aspects of elemental mercury vapour and inorganic compounds of mercury.

The major natural sources of mercury (Fig. 1) are degassing of the earth's crust, emissions from volcanoes, and evaporation from natural bodies of water (National Academy of Sciences, 1978; Nriagu, 1979; Lindqvist et al., 1984). The most recent estimates indicate that natural emissions amount to 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.

## 3.2 Man-Made Sources

The world-wide mining of mercury is estimated to yield about 10 000 tonnes/year, but this figure varies considerably from year to year, depending on the commercial value of the metal. Mining activities also 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 man-made sources are the combustion of fossil fuels, the smelting of metal sulfide ores, the production of cement, and refuse incineration. Using Sweden as a specific example (Swedish

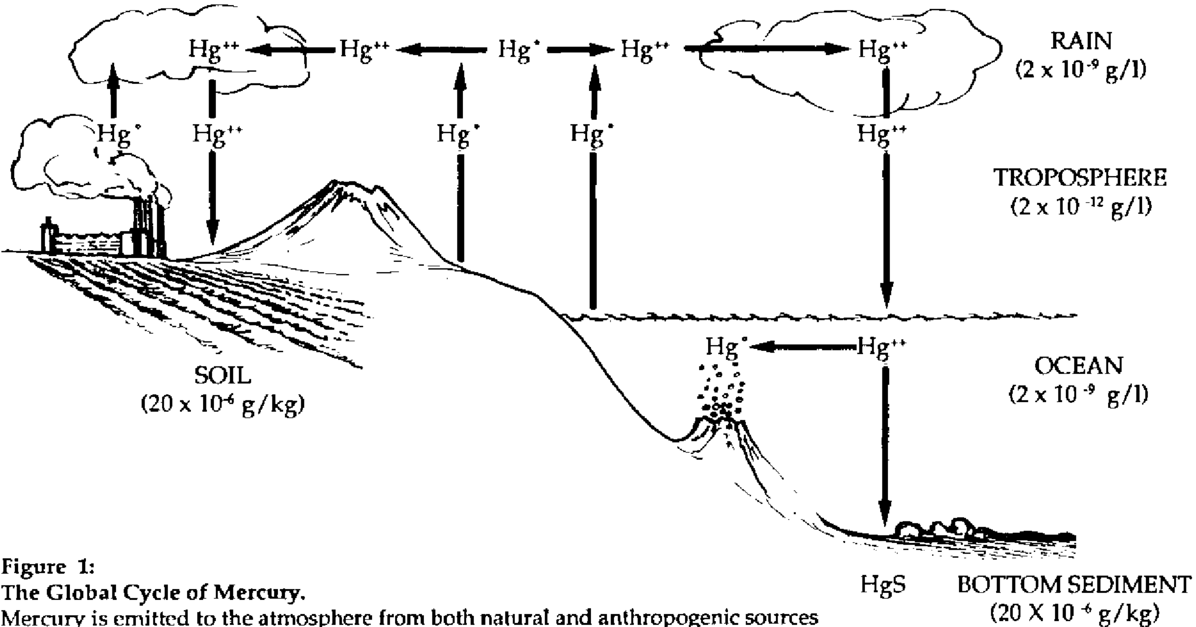


**Figure 1:**
**The Global Cycle of Mercury.**
Mercury is emitted to the atmosphere from both natural and anthropogenic sources in the form of elemental vapor ($Hg^{\circ}$). It is converted to a soluble form assumed to be $Hg^{++}$. The latter is returned to the surface of the earth in rain water and may be reduced to $Hg^{\circ}$ and re-emitted to the atmosphere. Ocean sediment is believed to be the final sink where mercury is deposited in the form of HgS.
The values for concentrations are taken from Lindquist et al (1984).

Environmental Protection Board, 1986), the mercury emissions to the atmosphere in 1984 were (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).

The total man-made global release to the atmosphere has been estimated to be 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 as to be near the limit of detection of current analytical methods, even for the determination of total mercury.

Anthropogenic releases of mercury into confined areas can be the source of high toxicity risk even though these releases may be small relative to global emissions. The point is relevant to the contamination of Minamata Bay and the Agano River in Niigata, Japan, as well as to inadvertent poisoning via contaminated bread in Iraq.

## 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. Quantities of the order of 10 tonnes of liquid metal are used in each manufacturing plant. In most industrialized nations, 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. In certain countries, liquid metallic mercury is still used in gold extraction. Mercury compounds continue to be used in anti-fouling and mildew-proofing paints and to control fungal infections of seeds, bulb plants, and vegetation. WHO has warned against the use of alkylmercury compounds in seed dressing (WHO,

1976a). Methylmercury compounds are still used in laboratory-based research, and so the possibility of occupational exposures remains (Junghans, 1983).

# 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

## 4.1 Transport and Distribution Between Media

Human exposure to mercury should first be viewed in the context of the world-wide circulation of this highly mobile metal (Fig. 1). The vapour of metallic mercury, hereinafter referred to as mercury vapour or $Hg^o$, is released into the atmosphere from a number of natural sources (section 3.1). Man-made emissions, mainly from the combustion of fossil fuels, form about 25% of the total emissions to the atmosphere. However, the anthropogenic contribution is greater in the northern than in the southern hemisphere and becomes the major form of emission in heavily industrialized areas, such as western Europe. The distribution constants of various mercury compounds between air and water are given in Table 2. Clearly, $Hg^o$ and dimethylmercury ($(CH_3)_2Hg$), as a result of their air/water distribution coefficients, are most likely to be found in the atmosphere.

Table 2. Experimentally determined distribution constants for some compounds of relevance for the mercury cycle[a]

| Compound | HgX (air)/ HgX (water) (v/v) | Temperature (°C) | $Cl^-$ ionic strength (mol) |
|---|---|---|---|
| $Hg^o$ | 0.29 | 20 | 0 |
| $(CH_3)_2Hg$ | 0.31 | 25 | 0 |
| $(CH_3)_2Hg$ | 0.15 | 0 | 0 |
| $CH_3HgCl$ | $1.9 \times 10^{-5}$ | 25 | 0.7 |
| $CH_3HgCl$ | $1.6 \times 10^{-5}$ | 15 | 1 |
| $CH_3HgCl$ | $0.9 \times 10^{-5}$ | 10 | $0.2 \times 10^{-3}$ |
| $Hg(OH)_2$ | $3.2 \times 10^{-6}$ | 25 | $0.2 \times 10^{-3}$ |
| $Hg(OH)_2$ | $1.6 \times 10^{-6}$ | 10 | $0.2 \times 10^{-3}$ |
| $HgCl_2$ | $2.9 \times 10^{-8}$ | 25 | $0.2 \times 10^{-3}$ |
| $HgCl_2$ | $1.2 \times 10^{-8}$ | 10 | $0.2 \times 10^{-3}$ |

[a] Adapted from: Lindqvist et al. (1984).

The solubility of mercury vapour in water is not high enough to account for the concentrations of mercury found

in rain water. Thus, Lindqvist et al. (1984) suggested that a small fraction of mercury vapour is converted to a water-soluble species, probably $Hg^{++}$, which is deposited on land and water in rain. However, the putative water-soluble forms have yet to be positively identified. Particulate forms account for less than 1% of total mercury in the atmosphere but may make an important contribution to mercury in rain water. The residence time of mercury vapour is estimated to be between 0.4 and 3 years, and as a consequence, mercury vapour is globally distributed. The soluble form is assumed to have a residence time of the order of weeks, and therefore the distance over which it may be transported is limited. The extremely low concentrations in the atmosphere (section 5.1.1) present formidable difficulties both in the analysis of total mercury and in the identification and measurement of chemical and physical species. For example, methylmercury compounds have been reported in the air above polluted areas in the USA (WHO, 1976b), but their presence in unpolluted air still needs to be confirmed. Shimojo et al. (1976) found methyl donors in car exhaust gases, but not methylmercury in the ambient air.

Mercury deposited on land and open water is, in part, re-emitted to the atmosphere as $Hg^{o}$. This emission, deposition, and re-emission ("ping-pong" effect) creates difficulties in tracing the movement of mercury to its source. The bottom sediment of the oceans is thought to be the ultimate sink where mercury is deposited in the form of the highly insoluble mercuric sulfide.

Recently, an expert group suggested that atmospheric mercury vapour could be taken up directly by plant foliage and that this might be an important pathway to watersheds in highly forested areas (Lindberg et al., 1987).

## 4.2 Biotransformation

Despite the uncertainties concerning speciation, the global cycle of mercury is believed to involve almost exclusively the inorganic forms. These forms do not accumulate in human food chains except in uncommon items, such as mushrooms (Minagawa et al., 1980). The change in speciation from inorganic to methylated forms is the first crucial step in the aquatic bioaccumulation process.

Methylation takes place mostly on sediments in fresh and ocean waters but also in columns of fresh and sea waters (Lindberg et al., 1987). Fish intestinal contents (Rudd et al., 1980) and the outer slime of fish have also been found to methylate inorganic mercury (McKone et al., 1971; Jernelov, 1972; Rudd et al., 1980).

The mechanism of synthesis of methylmercury compounds (both $CH_3Hg^+$ and $(CH_3)_2Hg$) is now well understood (Wood & Wang, 1983). Methylation of inorganic mercury involves the non-enzymic methylation of $Hg^{++}$ by methyl cobalamine compounds (analogues of vitamin $B_{12}$) that are produced as a result of bacterial synthesis. However, other pathways, both enzymic and non-enzymic, may play a role (Beijer & Jernelov, 1979). Factors affecting the aquatic methylation of mercury have been described by Fujiki & Tajuma (1975).

Microorganisms have also been isolated that carry out the reverse reactions:

$$CH_3Hg^+ \rightarrow Hg^{++} \rightarrow Hg^o$$

The enzymology of $CH_3Hg^+$ hydrolysis and mercuric ion reduction is now understood in some detail (Silver, 1984; Begley et al., 1986), as is the oxidation of mercury vapour to $Hg^{++}$ by an enzyme that is critical to the oxygen cycle (catalase). These oxidation-reduction and methylation-demethylation reactions are assumed to be widespread in the environment, and each ecosystem attains its own steady state with respect to the individual species of mercury. However, owing to the bioaccumulation of methylmercury, methylation is more prevalent in the aquatic environment than demethylation.

Once methylmercury is released from microorganisms, it enters the food chain by rapid diffusion and tight binding to proteins in aquatic biota. The results of a field study on the entry of methylmercury to the tuna food chain in the Mediterranean Sea fits the diffusion model (Bernhard et al., 1982).

Methylmercury is rapidly accumulated by most aquatic biota and attains its highest concentration in the tissues of fish at the top of the aquatic food chain (Bernhard et al., 1982). Thus, large predatory species, such as trout,

pike, walleye, and bass in fresh water and tuna, swordfish, and shark in ocean water, contain considerably higher levels than non-predatory species (Table 3). The ratio of the concentration of methylmercury in fish tissue to that in water can be extremely large, usually of the order of 10 000 to 100 000 (US EPA, 1980). However, it should be noted that these bioconcentration ratios are not the result of partition between water and tissue but of biomagnification through the food chain. In addition to the influence of trophic level or species, factors such as the age of the fish, microbial activity and mercury in sediment (upper layer), dissolved organic content (humic content), salinity, pH, and redox potential all affect the levels of methylmercury in fish (WHO, 1989a). Methylmercury in freshwater fish is also affected by the catchment area of the lake and by recent flooding or diversion of rivers (see section 4.3).

## 4.3 Interaction with Other Physical, Chemical, or Biological Factors

Following the identification of point sources of mercury pollution in the 1960s (Swedish Expert Group, 1971), it was discovered in the early 1970s that numerous lakes in Sweden had increased levels of methylmercury in pike, even though these lakes had not been subjected to any direct discharge of mercury. It was suggested by Hultberg & Hasselrot (1981) that three explanations should be considered:

- mercury discharged into the atmosphere is washed down by precipitation or is deposited (in the dry form) in the lake;
- acid precipitation causes the release of natural mercury or mercury deposited earlier by air that had been trapped;
- acidity in lakes induces a change in the biological dynamics of the lakes, which results in a re-distribution of mercury in the ecologic system.

The long-distance transport of mercury and the potential role of acidification have become major factors concerning future human exposure to methylmercury. Low pH

Table 3. The range of published average values of methylmercury (mg mercury/kg wet weight) in the muscle tissue of various species of fish[a,b]

| Species | Atlantic Ocean | Pacific Ocean | Indian Ocean | Mediterranean Sea |
|---|---|---|---|---|
| *Non-predators* | | | | |
| Mackerel | 0.07 - 0.2 | 0.16 - 0.25 | 0.005 | 0.24 |
| Sardine | 0.03 - 0.06 | 0.03 | 0.006 | 0.15 |
| Unspecified number of edible species | 0.08 - 0.27 | 0.07 - 0.09 | 0.02 - 0.16 | 0.1 - 0.3 |
| *Predators* | | | | |
| Tuna | 0.3 - 0.8 | 0.3 | 0.064 - 0.4 | 1.2 |
| Swordfish | 0.8 - 1.3 | 1.6 | - | 1.8 |
| Shark, dogfish, ray | 1.0 | 0.7 - 1.1 | 0.004 - 1.5 | 1.8 |

[a] Data from: US Department of Commerce (1978).
[b] Where an analysis of methylmercury was not available, the data on total mercury has been used instead.

favours both the direct uptake of methylmercury through the gills of fish and dietary uptake due to increased mercury accumulation by organisms in lower trophic levels (Wiener, 1987; Xun & Campbell, 1987). According to Hultberg and Hasselrot (1981), an increase in acidity of one pH unit in a lake increases the mercury content in pike by approximately 0.14 mg/kg wet weight. Wiener (1987) reported that a change of pH from 6.1 to 5.6 increased the mercury concentration in 1-year-old yellow perch from 0.11 $\pm$ 0.002 (SEM) mg/g to 0.138 $\pm$ 0.003 mg/kg within one calendar year. The causal relationship between reduction in pH and elevated mercury levels in edible tissues of fish has not been established. Possible mechanisms include:

- changes in population dynamics (a switch by pike from consumption of roach to consumption of perch);
- a reduction in the total biomass where most of the methylmercury is found (the growth of fish may be retarded and, for a given size, the mercury concentration will be higher);
- a low pH favours monomethyl versus dimethyl mercury; the latter is less avidly accumulated by fish;
- a low pH may elute more mercury from sediments or soils;
- as pH falls, the ratio of methylation to demethylation reactions increases, thus favouring an increase in the net production of methylmercury (Ramlal et al., 1986);
- Bjornberg et al. (1988) proposed that the concentration of the sulfide ion in water determines the bioavailability of inorganic mercury ($Hg^{++}$) and, therefore, the extent of methylation and uptake by aquatic organisms. A reduction in pH will reduce the concentration of the sulfide ion making more $Hg^{++}$ available for methylation.

Extensive investigations have been made in Canada in recent years to explain why methylmercury levels increase in fish when bodies of fresh water are relocated or redirected (Ramlal et al., 1985; Stokes & Wren, 1987). It

is proposed that the redirecting of rivers and the formation of reservoirs for hydroelectric production results in large quantities of organic material in the water, which serves as a food source for microorganisms. The resulting increase in microbial activity leads to an increase in the production of methylmercury from inorganic mercury naturally present in the sediment (Furutani & Rudd, 1980; Ramlal et al., 1986). This process is sustained by the repeated raising and lowering of water levels to maintain hydroelectric production, because the shorelines continue to be eroded and more vegetation enters the water. It is likely that future environmental impact statements will have to take into account this newly discovered source of methylmercury when hydroelectric schemes are planned.

As noted by Bjornberg et al. (1988), "many biological, chemical and physical factors are linked to each other in the limnic ecosystem" and "many of these factors seem to be of importance for the Hg content of fish". Thus "it is not difficult to understand why it has been considered hard to find simple mechanisms explaining why certain lakes have a high mercury content in fish and others have not". They propose that the "central piece in the puzzle" is the critical influence of the sulfide ion, which forms the highly insoluble mercuric sulfide with $Hg^{++}$ ($K_s = 10^{-52}$).

The solubility product of mercury selenide, HgSe, is even lower ($K_s = 10^{-58}$). Thus, studies made on a Canadian lake that had received a large discharge of inorganic mercury from a paper pulp factory suggest that the addition of selenite can reduce the availability of mercury for uptake into aquatic biota (Turner & Rudd, 1983). Studies on Swedish lakes confirm these findings (Björnberg et al., 1988). In these studies the selenium level was raised artificially from 0.4 to 2.4 μg/litre over a 1- to 2-year period, and the mean levels of mercury fell from 1.5 to 0.70 mg/kg in pike and from 0.56 to 0.16 mg/kg in perch. Such levels of selenium are below drinking-water standards.

# 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

## 5.1 Environmental Levels

There is considerable variation in mercury levels in those media that are the source of human exposure and, consequently, in their contribution to the toxicity risk. Non-occupational groups are primarily exposed through the diet. Although intake of the methylated form is of primary interest, levels of other species are summarized so as to provide a measure of total mercury intake.

### 5.1.1 *Air*

Concentrations of total mercury in the atmosphere of the northern hemisphere have recently been estimated at 2 $ng/m^3$, those in the southern hemisphere being half this value. Values in urban areas are usually higher (e.g., 10 $ng/m^3$) (Lindqvist et al., 1984). Schroeder & Jackson (1987) found values in the range 3-27 $ng/m^3$ (mean, 9 $ng/m^3$) in rural areas of Canada and 5-15 $ng/m^3$ (mean, 11 $ng/m^3$) in urban areas. In Sweden, urban levels appear to be slightly lower (range, 0.8-13.2 $ng/m^3$; mean, 4 $ng/m^3$).

Dental mercury fillings are reported to release mercury vapour into the oral cavity (Clarkson et al., 1988). The resulting concentrations in intra-oral air can substantially exceed those found in the ambient atmosphere, especially after of period of chewing. Estimates of pulmonary absorption indicate that approximately 3000-17 000 ng mercury vapour enter the systemic circulation daily from this exposure. As tobacco leaves contain mercury, smoking may also contribute to inhalation exposure (Suzuki et al., 1976).

As discussed in section 4.1, the major form of mercury in air is believed to be elemental mercury vapour. However, the presence of methylmercury compounds in the ambient atmosphere has been reported (Johnson & Braman, 1974). Recent data from the vicinity of Toronto, Canada, indicated the following average composition (as percentage of total mercury): $Hg^o$, 75%; $Hg^{++}$, 5%; and $CH_3Hg^+$, 20% (Schroeder & Jackson, 1987). The particulate fraction of

mercury in air (as a percentage of total mercury) is usually 4% or less (Lindqvist et al., 1984). The way in which the "soluble fraction" of mercury in air (section 4.1) relates to these recent findings on individual chemical species is still unclear.

### 5.1.2 Water

Concentrations of total mercury in natural water are so low that accurate analysis is still a major problem. Values for rain water are usually within the range 5-100 ng/litre, but mean values as low as 1 ng/litre have been reported. The most recent data (Fig. 1) indicate lower values than those previously recorded (WHO, 1976b). Representative values for dissolved total mercury are: open ocean, 0.5-3 ng/litre; coastal sea water, 2-15 ng/litre; freshwater rivers and lakes, 1-3 ng/litre. The concentration range for mercury in drinking-water is the same as in rain, with an average of about 25 ng/litre (Lindqvist et al., 1984).

The chemical speciation of mercury in water is still not completely defined. Mercury in ocean waters exists mainly in the form of $Hg^{++}$ complexed with chloride ions. Speciation in fresh water is poorly understood. In a contaminated lake system in Canada, methylmercury was found to constitute a varying proportion of total mercury, depending on the lake that was being tested, but, overall, accounted for approximately 1-6% of the total mercury (Canada-Ontario Steering Committee, 1983).

### 5.1.3 Food

Concentrations of mercury in most foodstuffs (WHO, 1976b; US EPA, 1984; Piotrowski & Inskip, 1981) are often below the reported limit of detection (usually 20 μg/kg fresh weight). Fish and fish products are the dominant source of methylmercury in food. The highest concentrations are found in both freshwater and marine fish at the highest trophic levels (Table 4). For example, shark and swordfish have average values of total mercury in edible tissues above 1200 μg/kg, whereas anchovies and smelt have average values below 85 μg/kg. Most other foodstuffs have average values below 20 μg/kg, with

mercury mainly in the inorganic form (Cappon, 1981; Gartrell et al., 1985a,b, 1986). Cappon (1987) reported mercury levels in vegetables.

## 5.2 General Population Exposure

### 5.2.1 *Estimated daily intakes*

The human intake of the three major forms of mercury present in the environment is summarized in Table 4. The intake of mercury from the ambient atmosphere has been estimated by assuming that the concentration of total mercury is 2 $ng/m^3$ and that 75% is present as elemental mercury vapour, 5% as inorganic mercury compounds, and 20% as methylmercury. The daily intake of each form of mercury was estimated by assuming a daily ventilation of 20 $m^3$, and the amount absorbed was estimated by assuming that 80% of the inhaled elemental vapour, 50% of the inorganic mercury compounds, and 80% of the methylmercury was absorbed across the pulmonary membranes (WHO, 1976b).

Mercury intake from drinking-water was estimated by assuming a daily water intake of 2 litres, an average concentration of 25 ng/litre, and that all the mercury is in the inorganic form. Methylmercury has been found in a few samples taken from bodies of natural water, but there have been no reports of methylmercury in drinking-water.

The intake of species of mercury in the diet was the most difficult to estimate. Total mercury intake from all foodstuffs in Belgium was 13 μg/day, compared with an intake from fish alone of 2.9 μg/day (Fouassin & Fondu, 1978). Also in Belgium, Buchet et al. (1983) measured a daily intake from all foodstuffs of 6.5 μg mercury.

The intake of total dietary mercury (μg/day) measured during a market basket survey (1984-1986) of the Food and Drug Administration (FDA) in the USA (Shibko, 1988), according to age group was: 0.31 (6-11 months); 0.90 (2 years); 1.76 (16 years, females); 1.84 (14-16 years, males); 2.32 (25-30 years, females); 3.01 (25-30 years, males); 2.29 (60-65 years, females) and 2.52 (60-65 years, males). It is of interest that when these intake rates are converted to μg/day per kg body weight, the values fall in a much more narrow range from 0.04 to 0.09. In fact

Table 4. 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] See text for assumptions underlying the calculations of average daily intake and retention.
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.

values for all the age groups except the two-year-olds fall between 0.044 and 0.054 μg/day per kg.

In Poland, the average daily dietary intake of mercury (estimated in 2134 duplicate portions) was 5.08 μg/day in the age group 1-6 years, 5.43 μg/day in the age group 6-18 years, and 15.8 μg/day in adults (Szprengier-Juszkiewicz, 1988). Owing to the low fish consumption (6.76 kg/year) and low mercury concentration in market fish (65 μg/kg), only 7% of the dietary intake derived from fish (Nabrzyski and Gajewska, 1984). Bernhard & Andreae (1984) estimated the world-wide mercury intake from seafood to be 2 μg/day, which is equivalent to a daily intake of 20 g seafood with a mercury concentration of 0.1 mg/kg. This agrees with estimates by a United Nations expert group (GESAMP, 1986). It should be pointed out that the individual variation in intake is large and that significant proportions of national populations have a mercury intake via seafood many times higher than the average (GESAMP, 1986).

For the purpose of estimating the average daily intake of total mercury and various mercury compounds (Table 4), it was assumed that the daily intake of total mercury from fish and fish products is 3 μg and that 20% of this is in the form of inorganic mercury compounds (i.e., 0.6 μg/day) and 80% is methylmercury (i.e., 2.4 μg/day). The intake of total mercury from non-fish sources was calculated as the difference between the average total dietary intake and the intake from fish. The average total dietary intake in the Belgium studies was $(6.5 + 13)/2 = 9.75$ μg/day, whereas the corresponding value for a 70-kg adult in the USA can be estimated from the FDA market basket survey as 3.5 μg. Taking the average of the Belgian and USA figures, the dietary intake of total mercury is estimated as $(9.75 + 3.5)/2 = 6.6$ μg/day. By subtracting from this figure the intake of methylmercury from fish (2.4 μg/day), the estimated total dietary intake of inorganic mercury is 4.2 μg/day. All the mercury from non-fish sources was assumed to be in the inorganic form. The amounts absorbed across the gastrointestinal tract were estimated on the assumption that 7% of the inorganic and 95% of the methyl species were absorbed (section 6).

The estimated dietary intake of inorganic mercury of 4.3 μg/day is the least reliable of the estimates in

Table 4. Data are not available on the species of mercury in most foodstuffs. In addition, the figures for dietary intake of total mercury come from only two countries - Belgium and the USA.

Table 4 portrays the relative magnitude of the contributions from various media. It is clear that fish and fish products are the dominant source of human exposure to methylmercury, even when low fish consumption is assumed (as in Table 4). Daily methylmercury intake can vary over a wide range, depending on the amount of fish consumed and the methylmercury concentration in the fish (Table 5). A number of communities have been identified where individual intakes exceeded 200 $\mu$g mercury/day (WHO, 1976b, 1980; Turner et al., 1980; GESAMP, 1986). As it is assumed that 80% of this mercury is methylmercury and that 95% of the methylmercury is absorbed, the absorbed amount of methylmercury (>153 $\mu$g/day) will, in these cases, dominate the daily mercury exposure (Table 4). On the basis of general population surveys of fish consumption, it was estimated that in Australia 0.9% of the population eat more than 1000 g fish/week and that this corresponded to about 20 $\mu$g mercury/day (WGMF, 1980). In the USA, surveys of fish consumption (US Dept. Commerce, 1978) were used to estimate that, with no regulatory control of the mercury content of marketed fish, 99.81% of all respondents had an upper limit mercury intake lower than their personal allowable daily intake (based on 30 $\mu$g mercury/day for a 70-kg person) at a 95% level. An action level of 1 mg mercury/kg in fish for regulatory control would increase this percentage to 99.87% and an action level of 0.5 mg mercury/kg would increase it to 99.89%.

Dental mercury amalgams account for the major background intake of mercury vapour (Clarkson et al., 1988). It is possible that mercury liberated from the amalgam can dissolve in the saliva as inorganic mercury, but there are no published reports on this possibility. A detailed discussion of the release of mercury from dental amalgams will be found in the Environmental Health Criteria monograph on Inorganic Mercury, which is due to be published in 1990.

Table 5. Intake of methylmercury (µg/day) from fish with various methylmercury levels and at various rates of fish consumption[a]

| Consumption of fish (g/day) | Level of methylmercury in fish (µg/kg fresh weight)[b] | | | | |
|---|---|---|---|---|---|
| | 200 | 500 | 1000 | 2000 | 5000 |
| 5 | 1 | 2.5 | 5 | 10 | 25 |
| 20 | 4 | 10 | 20 | 40 | 100 |
| 100 | 20 | 50 | 100 | 200 | 500 |
| 300 | 60 | 150 | 300 | 600 | 1000 |
| 1000[c] | 200 | 500 | 1000 | 2000 | 5000 |

[a] Adapted from: WHO (1980).
[b] For methylmercury concentration in fish see Table 3.
[c] Data from GESAMP (1986) indicate that maximum intakes may equal 1000 g/day.

# 6. KINETICS AND METABOLISM

A considerable amount of information was available on the metabolism of methylmercury at the time when Environmental Health Criteria 1: Mercury was published (WHO, 1976b). This section will briefly review the information in that document and quote more recent data where appropriate.

## 6.1 Absorption

Methylmercury in the diet is almost completely absorbed into the bloodstream (WHO, 1976b). Animals studies (Walsh, 1982) indicate that age, including neonatal stage, has no effect on the efficiency of gastrointestinal absorption, which is usually in excess of 90% of the oral intake. Data on rats indicate rapid and virtually complete absorption of inhaled methylmercury vapour into the bloodstream (Fang, 1980).

## 6.2 Distribution

Methylmercury is distributed in the bloodstream to all tissues. Distribution is completed within about 4 days in human beings (Kershaw et al., 1980), but the time after a single dose for maximum levels to be reached in the brain is one or two days longer than for other tissues (Berlin, 1986). At this time, the total brain contains approximately 6% of the dose (Kershaw et al., 1980), which is very near to 10% of the body burden (WHO, 1976b). These blood and brain values correspond to a six times higher concentration in the brain than in blood (Berlin, 1986). There are significant species differences in brain-to-blood ratios. After the prolonged administration of methylmercury, brain-to-blood ratios are between 3 and 6 in squirrel monkeys (Berlin, 1986) but somewhat lower in macaque monkeys (Evans et al., 1977). The ratio is generally low in non-primate animals, except in pigs (where it is 3.3); it is 1.5 in guinea-pigs, 1.2 in mice, and 0.06 in rats (Magos, 1987). Sex differences in distribution and retention have been reported in rats dosed with methylmercury (Magos et al., 1981; Thomas et al., 1986) and in both

adult (Hirayama & Yasutake, 1986) and prenatally exposed mice (Inouye et al., 1986).

There are also species differences in the distribution of methylmercury between erythrocytes and plasma. After the ingestion by human volunteers of fish containing methylmercury, the background-corrected erythrocyte-to-plasma methylmercury concentration ratio was about 20 (Kershaw et al., 1980). The ratio is approximately the same in monkeys and guinea-pigs, 7 in mice, and more than 100 in rats (Magos, 1987).

The blood-to-hair ratio in humans is about 1 to 250, but appreciable individual differences have been found (Table 6). Similarly, large individual differences exist in the ratio of cord blood to maternal blood concentration. Cord blood usually has somewhat higher methylmercury concentration than maternal blood (WHO, 1976b). Thus, in a group of Japanese women the average ratio of cord blood to maternal blood methylmercury concentration ranged from 0.8 to 2.8, with a mean of 1.65 (Suzuki et al., 1984b). The results of studies on rats (Ohsawa et al., 1981) and pigs (Kelman et al., 1980, 1982) indicate that placental transport of methylmercury into the fetus increases dramatically towards the end of pregnancy.

## 6.3 Metabolic Transformation

Methylmercury is converted to inorganic mercury, assumed to be $Hg^{++}$, in mammals (WHO, 1976b). The fraction of total mercury present in the tissues as $Hg^{++}$ depends on the duration of exposure to methylmercury and the time after cessation of exposure.

The percentage of total mercury present as $Hg^{++}$ in the tissues and body fluids of people exposed to high oral daily intakes of methylmercury for about 2 months in the Iraqi outbreak were: whole blood, 7%; plasma, 22%; breast milk, 39%; and urine, 73% (Amin-Zaki et al., 1976; Magos et al., 1976; WHO, 1976b). Measurements of liver tissues from fatalities in Iraq revealed that 16-40% was present as inorganic mercury. Unfortunately, no other tissues were available for analysis. There is a possibility that exposure to other mercury compounds may have occurred in some members of the Iraqi population.

Table 6. Relationship between mercury concentrations in the blood and hair of people with long-term exposure to methylmercury from fish

| Country | Number of subjects | Whole blood (x) (µg/litre) | Hair (y) (mg/kg) | Linear regression | Reference |
|---|---|---|---|---|---|
| Canada | 339 | 1 - 60 | 1 - 150 | y = 0.30x + 0.5 | Phelps et al. (1980) |
| Japan | 45 | 2 - 800 | 20 - 325 | y = 0.25x + 0 | WHO (1976b) |
| Netherlands | 47 | 1 - 40 | 0 - 13 | y = 0.26x + 0 | Den Tonkelaar et al. (1974) |
| Sweden | 12 | 4 - 650 | 1 - 180 | y = 0.28x - 1.3 | WHO (1976b) |
| | 51 | 4 - 110 | 1 - 30 | y = 0.23x + 0.6 | WHO (1976b) |
| | 50 | 5 - 270 | 1 - 56 | y = 0.14x + 1.5 | WHO (1976b) |
| | 60 | 44 - 550 | 1 - 142 | y = 0.23x - 3.6 | WHO (1976b) |
| United Kingdom | 173 | 0.4 - 26 | 0.1 - 11 | y = 0.25x + 0.6 | Haxton et al. (1979) |
| | 98 | 1.1 - 42 | 0.2 - 21 | y = 0.37x + 0.7 | Sherlock et al. (1982) |
| Yugoslavia | 38 | 1.2 - 9.6 | 0.4 - 3.0 | y = 0.34x - 22 | Horvat et al. (1986b) |

In Canadian Indians repeatedly exposed to methylmercury in fish during the summer season every year, inorganic mercury accounted for about 5% of total mercury in whole blood and about 20% in samples of head hair (Phelps et al., 1980). Brain mercury levels were measured in one Indian who had died of natural causes 2 years after having a high blood level (approximately 600 μg/litre). Most of the mercury in the brain tissue was in the inorganic form, but, at the time of his death, the total mercury in the brain had fallen to near background levels (Wheatley et al., 1979).

Following the outbreak in Minamata, Japan, in 1956, tissues from a number of early fatalities were analysed (Tsubaki & Takahashi, 1986). Death occurred between 19 and 100 days after the onset of symptoms. Tissues were also analysed from people who died from 1 to 17 years after the onset of symptoms. Samples were analysed initially by the dithizone colorimetric procedure in 1956-1960 and again in 1973-1983 by atomic absorption for total mercury and by gas chromatography for methylmercury. In this study, atomic absorption generally gave higher values for total mercury than the dithizone method. The methylmercury concentration was always less than that of total mercury, usually less than 50%, and in a few cases less than 10%. The chemical nature of the mercury not accounted for as methylmercury was not determined. It may, in whole or in part, have been methylmercury that could not be extracted in the gas chromatographic procedure, or it may have been inorganic mercury.

Speciation of mercury in human brain has been studied by Friberg et al. (1986) and Nylander et al. (1987). An average of 80% of the mercury in the occipital lobe cortex of autopsy cases in Sweden was found to be inorganic mercury (3-22 ng/g wet weight). Exposure to mercury from dental fillings could explain the high proportion of inorganic mercury in some cases but not in all.

There is considerable evidence indicating the presence of inorganic mercury in the tissues of animals dosed with methylmercury (WHO, 1976b). Magos & Butler (1972) showed that during long-term daily dosing, the fraction of inorganic mercury in rat tissues tended to approach a constant value, which was different for each tissue. The kidney and

liver had the highest fractions, while the brain had one of the lowest. Speciation of mercury in the brain of monkeys exposed to methylmercury for several years was studied by Lind et al. (1988b). At the end of the exposure period, 10-30% of the brain mercury was in the inorganic form while in monkeys sacrificed 0.5-2 years after the same treatment, about 90% was in the inorganic form. Similar observation was reported by Kawasaki et al. (1986), but in the cerebrum a substantially higher proportion of the total mercury was methylmercury than in the cerebellum (See also WHO, 1976b). It is clear that the proportion of inorganic mercury found at any time in a particular tissue will be determined by a number of processes, e.g., the relative rates of uptake and loss of inorganic mercury and methylmercury and the extent of biotransformation (if any) in that tissue. Studies by Suda & Takahashi (1986) indicate that macrophage cells, such as those present in the spleen, are capable of converting methylmercury to inorganic mercury. The reaction may involve the production of oxygen free-radicals. At present there are no definitive data that prove that demethylation actually takes place in brain tissue, but persuasive arguments have been presented by Lind et al. (1988b).

The conversion of methylmercury to $Hg^{++}$ may be a key step in the processes of excretion. The faecal pathway accounts for about 90% of the total elimination of mercury in man and other mammals after exposure to methylmercury (WHO, 1976b). Virtually all the mercury in human faeces is in the inorganic form (Turner et al., 1975). The process of faecal elimination begins with the biliary secretion of both methylmercury and $Hg^{++}$, complexed mainly, if not entirely, with glutathione (GHS) (Refsvik & Norseth, 1975) or other sulfhydryl peptides (Norseth & Clarkson, 1971; Ohsawa & Magos, 1974). Inorganic mercury is poorly absorbed across the intestinal wall (WHO, 1976b) so that most (approximately 90%) of the inorganic mercury secreted in bile passes directly into the faeces. Methylmercury secreted into the intestinal contents is in large part reabsorbed into the bloodstream and may subsequently contribute to biliary secretion, thereby forming a secretion-reabsorption cycle (Norseth & Clarkson, 1971). This cycle (also called enterohepatic circulation) increases the amount of methylmercury passing through the

intestinal contents and thus provides a continuous supply of methylmercury to serve as a substrate for the intestinal microflora. These microorganisms are capable of converting methylmercury to inorganic mercury, which then becomes the major contributor to total faecal elimination in the rat (Rowland et al., 1980). Presumably about 10% of the inorganic mercury produced by the intestinal microflora is absorbed into the bloodstream and contributes to the inorganic mercury concentrations in tissues, plasma, bile, breast milk, and urine. This intestinal microbiological activity may explain the influence of diet on methylmercury elimination rates in rats (Rowland et al., 1984, 1986), and the absence of demethylating intestinal microflora may be the reason for the low rate of faecal elimination of mercury in suckling mice (Rowland et al, 1983).

To what extent this model of enterohepatic circulation and intestinal conversion to inorganic mercury applies to humans is not yet known. Considerable species differences exist in rates of biliary excretion (Naganuma & Imura, 1984). Though the species variation in the secretion of methylmercury does not entirely correspond to the biliary excretion of GSH, high GSH secretion (rat, mice, and hamster) is associated (on a group basis) with high methylmercury secretion and low GSH secretion (guinea-pig and rabbit) with low methylmercury secretion (Stein et al., 1988).

Animal studies suggest that multigeneration exposure to methylmercury may change tissue distribution and metabolism (Yamamoto et al., 1986).

## 6.4 Elimination and Excretion

The rate of excretion of mercury in both humans and laboratory animals dosed with methylmercury is directly proportional to the simultaneous body burden, and therefore may be described by a single biological half-time (WHO, 1976b). The reason is that methylmercury is so mobile in the body that the excretion process is the rate-limiting step. Data on biological half-times in human beings were summarized in Environmental Health Criteria 1: Mercury (WHO 1976b). Kershaw et al. (1980) and Sherlock et al. (1984) reported half-times of 52 (39-67) and 50

(42-70) days in blood, close to the valves found earlier in people who ate fish or had consumed contaminated bread (WHO, 1976b). The whole-body half-times, determined in volunteers given a single tracer dose, have an average value of about 70 days and a range of 52-93 days. Only 20 subjects have been studied to date. Biological half-times in blood and hair have been measured both in volunteers given carefully measured doses and, after cessation of exposure, in individuals exposed as a result of accidental intake or high fish consumption. Observations on volunteers reveal values for blood half-time close to 50 days and a range of 39-70 days. Results from single tracer doses agree well with those from volunteers given measured doses in fish. It is clear that the blood half-times overlap those for the whole body, but the average value is lower. A shorter blood half-time would account for the observation that the amount of methylmercury in blood constitutes a decreasing fraction of the body burden with time after a single tracer dose (Miettinen, 1973). Lactating women have significantly shorter half-times (average value, 42 days) than non-lactating women (average value, 79 days), an observation confirmed by animals studies (Greenwood et al., 1978).

Observations on both volunteers and environmentally exposed people indicate that half-times in hair closely follow those in blood (Amin-Zaki et al., 1976; Kershaw et al., 1980; Hislop et al., 1983). However, hair half-times tend to have a wider range; for example, Al-Shahristani & Shihab (1974) reported a bimodal distribution in 48 Iraqi subjects, 90% having a half-time of 35-100 days and the other 10% a half-time of 110-120 days. It is possible, but not proven, that analytical artifacts may contribute to the wider range seen with hair (WHO, 1980). In any case, data from animals point to the importance of sex, age, and genetically determined individual differences (Hirayama & Yasutake, 1986).

Animal data indicate major ontogenic effects on biological half-times (Doherty et al., 1977). Suckling mice are completely unable to excrete methylmercury. At the end of the suckling period, excretion abruptly switches on at the adult rate. Observations on infant monkeys confirm this finding (Lok, 1983). Likewise, biliary secretion of methylmercury in suckling animals is virtually absent and

assumes the adult rate after weaning. It is of interest that biliary secretion of glutathione (GHS) shows parallel ontogenic changes (Ballatori & Clarkson, 1985). Microflora also have greatly diminished capacity to demethylate methylmercury during the suckling period (Rowland et al., 1983). In view of the failure of infant animals to excrete methylmercury, human infants may also have a diminished excretion. Unfortunately, no direct observations have yet been reported.

## 6.5 Retention and Turnover

The evidence summarized in section 6.4 indicates that the accumulation and excretion of methylmercury in humans, measured in terms of hair or blood levels, can be represented by a single-compartment model. The accumulation phase in the whole body or in a tissue compartment is described by the equation:

$$A = (a/b)(1-\exp(-b \times t)) \qquad \text{(equation 1)}$$

where $A$ = the accumulated amount
$a$ = the amount taken up by the body (or organ) daily
$b$ = the elimination constant
$t$ = time

The elimination constant is related to the biological half-time ($T_{\frac{1}{2}}$) by the expression:

$$T_{\frac{1}{2}} = \ln 2/b \qquad \text{(equation 2)}$$

and $a$ is related to the daily dietary intake ($d$) by the expression:

$$a = f \times d \qquad \text{(equation 3)}$$

where $f$ is the fraction of the daily intake taken up by the body (or organ).

At a steady state, the accumulated amount ($A$) is given by:

$$A = a/b \qquad \text{(equation 4)}$$

while the steady-state mercury concentration in blood ($C$) in $\mu$g/litre is related to the average daily dietary intake (in $\mu$g mercury) as follows:

$$C = f \times d/b = \frac{0.95 \times 0.05 \times d}{0.01 \text{ days}^{-1} \times 5 \text{ litres}} = 0.95 \times d \quad \text{(equation 5)}$$

assuming that 0.95 of the intake is absorbed, that 0.05 of the absorbed amount goes to the blood compartment, that the blood volume is 5 litres, and that the elimination constant is 0.01 days$^{-1}$.

Sherlock et al. (1984) tested the validity of equation 1 by measuring blood mercury concentrations during a 100-day period of methylmercury intake and a 100-day period after intake ceased in 20 volunteers who consumed measured daily amounts of methylmercury in fish. Close agreement was found between predicted and observed values.

Equation 1 predicts that a steady state in which intake equals excretion will be attained in about 5 half-times. Thus, in adult humans, the whole body would attain a steady state in about one year (5 x 70 days = 350 days). Thus, an important prediction of the single-compartment model is that constant dietary exposure to methylmercury for a period of several years should not result in any greater accumulation than after one year of exposure.

Equation 4 predicts that the maximum amount accumulated in the whole body of adult humans will be 100 times the average daily intake. In fact, steady blood levels may also be calculated from equations 2, 3, and 4, using the kinetic parameters to the single-compartment model listed in Table 7.

It is of interest to compare this predicted relationship with those observed in field studies on populations believed to have attained a steady state from long-term dietary exposure to methylmercury in fish (Table 7). The coefficients relating long-term dietary intake to steady-state blood concentration are all lower than the predicted value of 0.95 calculated in equation 5 above. The reasons for this discrepancy are not yet fully understood. The

Table 7. Relationship between steady-state blood concentrations and average daily intake of methylmercury in fish consumers and predicted relationships from experimental data

| Number of subjects | Duration of exposure | Average mercury intake (µg/day per 70 kg body weight) ($x$) | Steady-state blood concentration (µg mercury/litre) ($y$) | Reference |
|---|---|---|---|---|
| *Observed relationship* | | | | |
| 32 | years | 0 - 800 | $y = 0.7x + 1$ | WHO (1976b) |
| 165 | years | 0 - 400 | $y = 0.3x + 5$ | WHO (1976b) |
| 20 | years | 0 - 800 | $y = 0.8x + 1$ | WHO (1976b) |
| 725 | years | 0 - 800 | $y = 0.5x + 4$ | WHO (1976b) |
| 22 | years | 0 - 800 | $y = 0.5x + 10$ | WHO (1976b) |
| *Predicted relationship* | | | | |
| 15 | 1 dose | tracer | $y = 1x$ | WHO (1976b) |
| 30 | 1 - 2 months | 0 - 2340 | $y = 0.8x$ | WHO (1976b) |
| 5 | 1 dose | 1400 | $y = 1x$ | Kershaw et al. (1980) |
| 20 | 100 days | 0 - 230 | $y = 0.8x$ | Sherlock et al. (1984) |

measurement of dietary intake in populations with uncontrolled intakes is liable to considerable error (Turner et al., 1980). However, this would not explain the consistently lower values from field studies. It is more likely that these populations were not in true steady state, since intake is frequently seasonal in fish-eating populations. The fact that close agreement is seen between single-dose tracer studies, single-dose methylmercury intake from fish, extended controlled intake from fish, and longitudinal hair analysis of individuals with very high intakes lends support to the validity of the single-compartment model and the values of the kinetic parameters listed in Table 8. Sherlock and Quinn (1988) presented a more detailed discussion of the differences between controlled and uncontrolled studies on the relationship between blood concentration and intake of methylmercury.

It should be emphasized that this model refers to the "average" adult human with a body weight of 70 kg. The gastrointestinal absorption rate for methylmercury is high (about 95%) and is not known to vary with age, but the energy intake varies greatly with age and this tends to make children and teenagers more vulnerable to high intakes of methylmercury.

The one compartment model is a useful working model for comparing blood or hair levels to daily intakes of methylmercury. Clearly this model is only an approximation to the more complex kinetics of mercury distribution and metabolism. For example, determination of mercury in hair and blood will not produce information concerning small compartments in the body. Methylmercury is slowly transformed to inorganic mercury, a process which is known to follow multiphasic kinetics (Berlin, 1986).

## 6.6 Reference or Normal Levels in Indicator Media

Reference values in non-exposed populations for concentrations of total mercury in commonly used indicator media are given in Table 9. The mean concentration in whole blood is probably about 8 μg/litre, in hair about 2 μg/g, in urine 4 μg/litre, and in the placenta about 10 μg/g wet weight.

Table 8. Principal kinetic parameters in the single-compartment model for methylmercury in adult human beings

| Number of subjects | Type of subject | Dose (µg mercury/kg) | Number of doses | Compartment | | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | Whole body | | Blood | | |
| | | | | *f* | *T*½ (days) | *f* | *T*½ (days) | |
| 3 | adult | tracer | 1 | 0.95 | 72 | - | - | WHO (1976b) |
| 15 | adult | tracer | | 0.94 | 76 | 0.07 | 50 | WHO (1976b) |
| 5 | adult | 20 | 1 | - | - | 0.05[a] | 52 | Kershaw et al. (1980) |
| 5 | adult | 3.3 | 100 | - | - | 0.05[a] | 53 | Sherlock et al. (1984) |
| 5 | adult | 1.5 | 100 | - | - | 0.055[a] | 51 | Sherlock et al. (1984) |
| 4 | adult | 100 | 100 | - | - | 0.057[a] | 48 | Sherlock et al. (1984) |
| 5 | adult | 0.6 | 100 | - | - | 0.064[a] | 46 | Sherlock et al. (1984) |

[a] Calculations were made from concentrations in blood. The value of *f* (fraction of dose which reached the compartment) was calculated assuming a blood volume of 5 litres in a 70-kg adult.

Table 9. Concentrations of mercury in indicator media in non-exposed populations[a]

| Country | Indicator media | No. of Subjects | Mercury concentration[b] | | Reference |
|---|---|---|---|---|---|
| | | | Mean | Range | |
| Belgium | placenta | 474 | 15 | 1.1 - 103 | Roels et al. (1978)[h] |
| | whole blood | 497 | 12 | 0.1 - 47 | Lauwerys et al. (1978) |
| Italy | whole blood | 80 | 20 | 0 - 46 | Pallotti et al. (1979) |
| Japan | maternal blood | 11 | 6.6 | 2.0 - 15.6[f] | Suzuki et al. (1984b) |
| | umbilical blood | 7 | 8.9 | 3.1 - 20.6[f] | Suzuki et al. (1984b) |
| New Guinea | hair | 40 | 4.5 | 0.9 - 12.1 | Suzuki et al. (1988) |
| Norway | urine | 206 | 4 | 0.6 - 71 | Lie et al. (1982) |
| Poland | whole blood | 270 | 11.3 | | Szucki & Kurys (1982) |
| | hair | 505 | 2.2 | | Szucki & Kurys (1982) |
| | Maternal hair | | | | |
| | (scalp) | 141 | 1.9 | 0.02 - 41 | Sikorski et al. (1986) |
| | (pubic) | 141 | 1.0 | ND-32 | Sikorski et al. (1986) |
| | Neonatal hair | 141 | 0.11 | ND-0.62 | Sikorski et al. (1986) |
| Sweden[c] | hair | 18 | 0.4 | | Ohlander et al. (1985) |
| | hair | 41 | 0.53 | | Forhammer et al. (1984) |
| United Kingdom | whole blood | 87 | 8.8[d] | 1.1 - 42 | Sherlock et al. (1982) |
| | urine | 77 | <10 | | Taylor & Marks (1977) |
| USA | whole blood | 210 | 8 | 0 - 50 | Gowdy et al. (1977) |
| | whole blood | 25 | 3.4 | 0 - 7[f] | Kuhnert et al. (1981) |
| | placenta | 25 | 6.7[e] | 0 - 13[f] | Kuhnert et al. (1981) |

Table 9 (contd).

| Country | Indicator media | No. of Subjects | Mercury concentration[b] | | Reference |
|---|---|---|---|---|---|
| | | | Mean | Range | |
| Yugoslavia | hair | 34 | 1.5 | 0.4 - 3.3 | Horvat et al. (1988b) |
| | maternal blood | 34 | 3.7 | 1.2 - 9.6 | Horvat et al. (1988b) |
| | umbilical blood | 34 | 7.7 | 1.2 - 21 | Horvat et al. (1988b) |
| | placenta | 34 | 13 | 2.8 - 37 | Horvat et al. (1988b) |
| Northern hemisphere[g] | hair | 312 | 3.1 | 0 - 9 | Airey (1983) |
| Northern hemisphere | hair | 4603 | 2.3 | 0 - 5 | Airey (1983) |
| Southern hemisphere | hair | 1449 | 1.7 | 0.8 - 2.5 | Airey (1983) |

[a] No known occupational exposure; fish consumption usually less than one meal per week.
[b] The units for mercury concentrations are: µg/kg for placenta, µg/kg for blood and urine, and mg/kg for hair. ND = not detectable.
[c] Pregnant women.
[d] Values are for adults; newborn values are 10-16% higher.
[e] The placentae were perfused to remove blood before analysis.
[f] Range estimated as twice the standard deviation.
[g] North of 22° latitude.
[h] This reference contains data on levels published prior to 1976.

Additional data on levels in indicator media in different populations are given in the following references: Belgium (Buchet et al., 1978), Canada (Galster, 1976; Kershaw et al., 1980; Phelps et al., 1980; McKeown-Eyssen & Ruedy, 1983a; McKeown-Eyssen et al., 1983; Valciukas et al., 1986), Federal Republic of Germany (Lommel et al., 1985), Finland (Mykkanen et al., 1986), Greenland (Hansen et al., 1984), Iceland (Johannesson et al.,1981), Italy (Capelli et al., 1986), the East Pacific area (Yamaguchi et al., 1977), Japan (Suzuki et al., 1984a), New Guinea (Kyle & Ghani, 1982a,b; 1983), New Zealand (Kjellstrom et al., 1982), Seychelles (Matthews, 1983), Spain (Gonzalez et al., 1985), and Sweden (Skerfving, 1974). Intake of methylmercury is reflected in elevated levels in whole blood and in erythrocytes (approximately 95% of blood mercury is in the erythrocytes). Animal studies indicate that, at non-toxic levels, blood methylmercury concentration is a good index of brain mercury concentration (Berlin, 1976).

Urine and blood concentrations correlate with mercury vapour levels only after long-term exposures (Smith et al., 1970). Blood levels rise and fall sharply during and after short-term exposures (Cherian et al., 1978).

Hair levels may be increased as a result of direct adsorption of mercury vapour onto the hair strands. Airey (1983) reported that the average hair mercury levels in the northern hemisphere are higher than in the southern hemisphere (Table 9).

Long-term fish consumption determines almost completely the concentrations of methylmercury and, usually, total mercury in blood. Thus, reference values must take into account fish consumption. In communities with high fish consumption rates, individuals with long-term intakes of 200 μg mercury/day will have blood levels in the range of 200 μg mercury/litre.

Hair concentrations of methylmercury are proportional to blood concentrations at the time of formation of the hair strand (Table 6). In general, the concentration in hair is 250 times the simultaneous concentration in blood. Once mercury is incorporated into a hair strand, that hair

mercury concentration remains unchanged. Thus, longitudinal measurement of mercury in hair provides a recapitulation of methylmercury levels in blood. Airey (1983) presented a comprehensive evaluation of mercury levels in hair. The author found that mean hair mercury concentrations corresponded to fish consumption patterns as follows: once or less a month, 1.4 μg/g; once every 2 weeks, 1.9 μg/g; once a week, 2.5 μg/g; and once or more a day, 11.6 μg/g. Owing to their higher-than-average fish consumption, fisherman may have higher-than-average methylmercury concentrations in their hair. For example, in three Mediterranean countries, (Greece, Italy, and Yugoslavia) 33% of 212 fishermen but only 0.33% of 918 other residents had methylmercury levels in hair above 10 μg/g (WHO/FAO/UNEP, 1989). These data support the conclusion that long-term fish intake determines methylmercury levels in hair and also in blood.

## 6.7 Reaction with Body Components

Information on the binding of methylmercury to tissue ligands other than haemoglobin is sparse. Methylmercury is believed to bind to cystinyl residues in the haemoglobin molecule. The number and position of these residues in the amino acid chains differ in haemoglobin from different species (Doi & Kobayashi, 1982, Doi & Tagawa, 1983). Methylmercury is complexed to glutathione (GHS) in both human and animal erythrocytes (Naganuma et al., 1980). The only known exception is rat erythrocytes where practically all methylmercury is bound to haemoglobin (Doi & Tagawa, 1983). Methylmercury complexes may also be involved in the urinary excretion of methylmercury (Mulder & Kostyniak, 1985a,b). Animal data indicate that methylmercury complexes also exist in brain tissue (Thomas & Smith, 1979; Berlin et al., 1975), bile (Refsvik & Norseth, 1975), liver (Omata et al., 1978), and probably in kidney tissue (Richardson & Murphy, 1975). Complexes of methylmercury with GHS and possibly other low molecular-weight thiols play a role in blood transport and tissue distribution (Hirayama, 1980; Thomas & Smith, 1982) and in biliary secretion (Ballatori & Clarkson, 1985; Urano et al., 1988). Glutathione-*S*-transferase (ligandin) may be involved in the biliary secretion process (Refsvik, 1984a,b; Magos et al., 1985b), but evidence is still

equivocal (Gregus & Varga, 1985). The activity of hepatic γ-glutamyltransferase may also affect methylmercury secretion in bile (Stein et al., 1988). According to *in vitro* studies, the transport of methylmercury across cell membranes appears to be a diffusional process involving an unchanged complex of methylmercury chloride (Lakowicz & Anderson, 1980; Bienvenue et al., 1984). However, the relevance of these findings to *in vivo* transport across membranes is not clear. Due to the high affinity of the methylmercury cation for sulfhydryl groups, it is unlikely that methylmercury chloride will be present in significant amounts in plasma or other biological fluids. Amino acid complexes may be involved in membrane transport of methylmercury (Hirayama, 1980, 1985; Aschner & Clarkson, 1987; Watanabe et al., 1988).

The administration of selenium compounds to animals protects against the toxic effects of methylmercury (Ganther et al., 1972; Iwata et al., 1973). It alters the tissue distribution and excretion of methylmercury (Ganther, 1978, Prohaska & Ganther, 1977) and also the inorganic-to-methyl mercury ratio in tissues (Komsta-Szumska & Miller, 1984; Brzeznicka & Chmielnicka, 1985a). In spite of the protective effect, selenite increases the brain concentration of methylmercury (Magos & Webb, 1977; Brzeznicka & Chmielnicka 1985b). The methylmercury cation has a high affinity for selenides and diselenides (Sugiura et al., 1978), the latter being formed by the reductive metabolism of selenite (Hsieh & Ganther, 1975; Ganther, 1979). It has been reported that $(CH_3Hg)_2Se$ can be formed both *in vitro* and *in vivo* (Magos et al., 1979; Naganuma & Imura, 1980; Masukawa et al., 1982). To what extent the formation of this compound explains the altered tissue distribution of methylmercury is not yet clear. Selenium may also divert mercury from its endogenous binding sites, but Thomas & Smith (1984) were not able to find evidence for this. Maternal administration of selenium to mice causes a specific alteration in the form of selenium in fetal liver, as indicated by gel filtration chromatography. This change was not found in maternal liver or kidney or in the placenta (Nishikido et al., 1988b).

# 7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Data concerning the effects of methylmercury on organisms in the environment are discussed in Environmental Health Criteria 86: Mercury - Environmental Aspects (WHO, 1989a).

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

Methylmercury is a systemic poison and, depending on the dose and the length of exposure period, can affect various organ systems and functions. However, in every species the main target is the nervous system and one of the earliest objective clinical signs is ataxia. The significance of effects on animals is confounded by well-established species differences in both the localization of nervous system damage and in accompanying clinical and pathological changes (Berlin, 1986). Another common target is the fetus. As methylmercury is capable of corrosive action, it can damage any tissue (skin, eye, upper part of the digestive tract) if presented in sufficiently high concentrations (WHO, 1976b).

## 8.1 Neurotoxicity and Nephrotoxicity

The effects of methylmercury given in a single lethal dose is uncharacteristic. After intraperitoneal administration, rats showed respiratory and vascular disorders and hamsters became comatose (Hoskins & Hupp, 1978), whereas after oral administration to pigs, central nervous system depression, ending in coma, was preceded by diarrhoea and vomiting (Piper et al., 1971). Rats surviving an $LD_{50}$ dose showed general debilitation with weight loss, but did not develop specific motorial changes, while a squirrel monkey that had survived the severe acute effects of a single dose (6.4 mg/kg) became uncoordinated by 22 days and blind at 24 days (Hoskins and Hupp, 1978).

The cause of weight loss is anorexia. The anorexic effect shows significant species differences. Anorexia precedes the clinical signs of nervous system injury in rodents treated daily with methylmercury (Magos, 1982). In cats (Davies & Nielsen, 1977) and dogs (Davies et al., 1977), anorexia and gait disorder ("bunny-hopping") occur simultaneously. In the squirrel monkey only severe methylmercury intoxication is associated with weight loss (Evans et al., 1977).

Studies on the neurotoxicity of methylmercury were reviewed by WHO (1976b). This review called attention to

species differences in blindness and the involvement of peripheral nerves. Blindness may be caused in man, monkeys, and pigs, but not in cats. In rats, the initial damage appears in the dorsal root ganglions and associated peripheral nerves, while in monkeys the cerebral cortex is the first target. One of the most common lesions of the central nervous system is in the granular layer of the cerebellum. This type of damage has been observed in man (Takeuchi & Eto, 1975) and also in rats, cats, hens (Chang, 1977), dogs (Davies et al., 1977), calves (Herigstad et al., 1972), guinea-pigs (Falk et al., 1974), and rabbits (Jacobs et al., 1977), but not in pigs (Davies et al., 1976) or monkeys (Chang, 1977; Mottet et al., 1987). Female rats, which accumulate higher concentrations of methylmercury in their brain than males, also develop more severe cerebellar lesions (Magos et al., 1981).

These experimental studies (see also Mitsumori et al., 1984 and Munro et al., 1980) confirmed clinical findings in human beings of irreversible damage to the nervous system. Other experimental studies carried out since the publication of Environmental Health Criteria 1: Mercury (WHO, 1976b), which focused on the mechanism of toxicity, are reported in section 9.3.1.3.

Renal damage is one of the most frequently described non-neural effect of methylmercury. This damage may be caused by inorganic mercury split from methylmercury. In rats, treatment with methylmercury caused renal damage ranging from ultrastructural changes to the degeneration of the distal convoluted tubules (see WHO, 1976b). Male rats are more sensitive to the renotoxic effect of methylmercury than females (Munro et al., 1980). Renal damage was also observed in other experimental species. In most of the dogs that showed clinical and histological signs of methylmercury-induced neurotoxicity, there were also signs of renal necrosis, desquamation, and regeneration (Davies et al., 1977). In the kidneys of methylmercury-intoxicated guinea-pigs, only swelled epithelial cells in the proximal tubules were reported (Falk et al., 1974). In cats (Davies & Nielsen, 1977) and pigs (Davies et al., 1976), only hyalin and cellular casts were seen. Though treatment of six monkeys (*Macaca mulatta*) with daily doses of methylmercury (80-120 μg mercury/kg in apple juice) for 3.5-12 months did not affect the general health status adversely,

it caused ultrastructural changes in the kidneys (Chen et al., 1983). These changes included intracytoplasmic vacuoles and electron-dense inclusion bodies. In the same studies, degenerative changes in the Paneth cells of intestines were also observed. These changes were most pronounced in animals killed immediately after exposure (see also Mottet et al., 1987).

## 8.2 Reproduction, Embryotoxicity, and Teratogenicity

Methylmercury added *in vitro* to a suspension of sperm from untreated monkeys *(Macaca fasicularis)* at 9-15 μg/ml decreased sperm motility but did not decrease oxygen consumption (Mohamed et al. 1986a,b). In fact, oxygen consumption was increased at the 15 μg/ml concentration when sperm motility was almost zero. Further studies with specific inhibitors revealed that mitochondrial energy production was not affected by mercury. The authors suggested that the primary effect was on the dynein/microtubule sliding assembly.

Lee & Dixon (1975) reported damage to spermatogenesis in mice given a methylmercury dose of 1 mg mercury/kg, much lower doses giving rise to neurological effects. No special susceptibility to sterility, resulting from prenatal exposure, could be detected in mice (Gates et al., 1986).

When female mice were given a single intraperitoneal injection of methylmercury chloride (2.5, 5, or 7.5 mg/kg body weight) prior to mating, dose-related increases in pre- and early post-implantation fetal losses were recorded (Verschaeve & Leonard, 1984). This observation could have a genetic cause or result from physiological effects on the mother.

Gunderson et al. (1986) treated 11 monkeys *(Macaca fasicularis)* with daily oral doses of methylmercury in apple juice (50-70 μg/kg per day) before and during pregnancy. The mean blood levels during pregnancy, measured in each trimester and at delivery, were within the range of 1080-1330 μg/litre, with maximum values within the range of 1510-1840 μg/litre. The mean blood levels of the offspring at birth were 1690 μg/litre (range, 880-2460 μg/litre). When tested 190 days post-conception, the

mean blood levels had fallen to 1040 μg/litre. The exposed animals showed recognition deficits (compared with 10 untreated controls) when administered an adaptation of a standardized test of visual recognition memory. The same blood mercury concentration (600-2000 μg/litre) in pregnant squirrel monkeys exposed to methylmercury resulted in a 22.5% (mean of six results) reduction in the cerebral weight of fetuses (Logdberg et al, 1988). Three months treatment with daily oral doses of methylmercuric hydroxide (50 or 90 μg/kg) increased the frequency of reproductive failure (i.e., non-conception, abortion) in non-human primates and decreased the birth weight of their offspring (Burbacher et al., 1984). Offspring from treated animals directed significantly less attention to novel stimuli than did controls.

At doses which are not toxic to the rat dam, prenatal exposure produced hydrocephalus, decreased thickness of the cerebral cortex in the parietal section, increased thickness of the hippocampus in the occipital region (Kutscher et al., 1985), and delayed ossification (Chmielnicka et al., 1985). A variety of structural changes, detectable at both the light and electron microscopic levels, were also observed by Reuhl et al., (1981a,b). Similar effects have been noted in prenatally exposed mice where the development of communicating hydrocephalus was associated causally with aqueductal stenosis (Choi et al., 1988).

Prenatal exposure at doses not affecting the mother is known to produce abnormal behaviour in the offspring of several animal species (Spyker et al., 1972; Bornhausen et al., 1980; Zimmer et al., 1980; Shimai & Satoh, 1985; Elsner et al., 1988). The behavioural effects may be the consequence of an effect on neurotransmitters in the brain. Thus a single dose of 5.0 mg mercury/kg, given as methylmercury on postnatal day 2, resulted in increased serotonin concentration and movement and postural disorders by day 22-24 (O'Kusky et al., 1988). In addition, Bartolome et al. (1982) showed both acute and long-lasting effects on the maturation of central catecholamine neurotransmitter systems following early postnatal exposure. Eccles & Annau (1982a,b) demonstrated altered behavioural sensitivity to amphetamine in adult offspring, and Cuomo

et al. (1984) showed alterations in response to apomorphine.

Prenatal exposure of rodents can produce a variety of effects on non-nervous tissues. It is well known that the administration of large doses of methylmercury to pregnant rodents produces cleft palate (e.g., Lee et al., 1979; Harper et al., 1981). Prenatal exposure of rats can produce renal functional abnormalities detectable in offspring at 42 days of age (Smith et al., 1983; Slotkin et al. 1986).

## 8.3 Mutagenicity and Related End-Points

Methylmercury is capable of causing chromosome damage in cell cultures (Morimoto et al., 1982; Curle et al., 1983), in the golden hamster (Watanabe et al., 1982; Gilbert et al., 1983), and in ovulating Syrian hamsters (Mailhes, 1983). It can induce histone protein perturbations (Gruenwedel & Diaham, 1982) and influence factors regulating the nucleolus-organizing activity (Verschaeve et al., 1983). The mutagenic response of V79 Chinese hamster cells to methylnitrosourea is enhanced by methylmercury (Onfelt & Jenssen, 1982). Methylmercury has been reported to interfere with gene expression in *in vitro* cultures of glioma cells at low concentrations (0.05-0.1 μmol/litre) (Ramanujam & Prasad, 1979). The induction of non-disjunction and sex-linked recessive lethal mutations was found in *Drosophila melanogaster* treated with methylmercury. Tolerance to methylmercury was correlated with the uptake of mercury and not with the rate of excretion (Magnusson & Ramel, 1986).

## 8.4 Carcinogenicity

Methylmercury has been reported to produce renal carcinomas in mice given diets containing methylmercury chloride (15 mg/kg) for about one year (Mitsumori et al., 1981). Animals given 30 mg/kg died from neurotoxicity after 6 months. Nixon et al. (1979) found that prenatal exposure to methylmercury increased the incidence in rats of neural tumours caused by sodium nitrite and ethylurea. The mothers had been exposed since weaning to 10 mg methylmercury/kg diet. These are the only reports of

potential carcinogenicity. Blakley (1984) administered methylmercury chloride to Swiss mice (0.2, 0.5, or 2 mg/litre drinking-water) for 15 weeks and gave them a single dose (1.5 mg/kg) of urethane by intraperitoneal injection at the end of the third week. Methylmercury produced a dose-related increase in the *size* of lung adenomas induced by urethane. However, only the highest dose (2 mg/kg) increased the *incidence* of adenomas. No effects on weight gain or water consumption related to methylmercury treatment were seen.

## 8.5 Special Studies

Kato et al. (1981) reported that the detection of electro-oculographic changes in monkeys is one of the most sensitive indices of methylmercury effects. Using high doses of methylmercury, Wassick & Yonovitz (1985) demonstrated auditory deficits over a 4- to 78-kHz frequency range in mice. Methylmercury is known to affect auditory performance in human beings (section 9.1).

Methylmercury has been found to depress both primary and secondary immune responses in rodents (Koller & Roan, 1980; Koller et al., 1980). Other effects reported in animal studies include impairment of adrenal and testicular function in rats (Burton & Meikle, 1980), impairment of thyroid function in mice (Kawada et al., 1980), and impairment of sleep-walking rhythms in rats (Arito et al., 1983). Effects of methylmercury on glucose transport, glucose metabolism, and blood flow in the central nervous system were described by Hargreaves et al. (1986).

Long-term treatment of Brown-Norway rats produces proteinuria (Bernaudin et al., 1981). This strain is genetically susceptible to immune-mediated renal damage produced by inorganic mercury.

## 8.6 Factors Modifying Toxicity; Toxicity of Metabolites

Several substances have been found to affect the chronic toxicity of methylmercury. Of these, selenium, usually administered to animals as sodium selenite, has been the most widely studied, following the first report by Ganther et al. (1972). In general, selenium has a protective action in that it delays the onset of

methylmercury toxicity or reduces the severity of its effects (Chang & Suber, 1982). Simultaneous administration of sodium selenite to mice during pregnancy was found to protect the offspring from effects on developmental reflexes caused by a 6 mg/kg dose of methylmercury given on day 9 (Satoh et al., 1985). In mice given selenium (11.6 nmol/ml in the drinking-water) before and after gestation, the incidence of methylmercury-induced resorption was increased. The incidence of cleft palate in mice was not affected by excess selenium (Nobunaga et al., 1979) nor by selenium deficiency (Nishikido et al., 1988a), but selenium deficiency enhanced the fetal toxicity of methylmercury (Nishikido et al., 1987).

Another antioxidant, vitamin E, has also been found to be protective against methylmercury toxicity in both normal and selenium-deficient rats (Chang et al., 1978; Welsh, 1979). The antioxidant *N,N′*-diphenyl-*p*-phenylylenediamine, however, was more protective than vitamin E. The latter also protected against the *in vitro* damage caused by methylmercury to chromosomes in human blood cells (Morimoto et al., 1982), hamster fibroblast cells (Gilbert et al., 1983), and glioma cells (Prasad & Ramanujam, 1980). Phospholipids have been reported to protect against the *in vitro* action of methylmercury on rat liver enzymes (Magnaval & Batti, 1980). The significance of these findings to human health is not clear, as high doses were used and methylmercury poisoning in rodents may not be the same as in human beings. Moreover selenite only delays the onset of methylmercury intoxication (Chang & Suber, 1982) and is not the form of selenium found in human diets. Though selenium in marine food may have the same protective action as selenite (Newberne et al., 1972; Ohi et al., 1980; Thrower & Andrewartha, 1981), the bioavailability of biological selenium for reaction with mercury is less than that of selenite (Magos et al., 1984) and its potential, free from other dietary effects, to delay the onset of methylmercury intoxication has not been proved.

Ethanol has been found to potentiate the effects of methylmercury in rats (Turner et al., 1981). This single finding should be investigated further, preferentially in primates, as it could have considerable public health significance.

Yamini & Sleight (1984) found that guinea-pigs on a diet deficient in vitamin C suffered more severe neurological damage when exposed to 44 mg methylmercury/kg in their diet for 20 days than controls fed a diet with adequate vitamin C.

It has been postulated that methylmercury might produce its effects via cleavage of the mercury-carbon bond (Ganther, 1978). This could produce free radicals, causing lipid peroxidation. This might explain the protective action of vitamin E and selenium. Inorganic mercury released from methylmercury might be the actual toxic species. However ethylmercury, which decomposes faster and raises inorganic mercury concentration in the brain to a higher level than does methylmercury, produces less brain damage at equal doses (Magos et al., 1985a).

# 9. EFFECTS ON MAN

## 9.1 General Population Exposure

The effects of methylmercury on the adult differ both quantitatively and qualitatively from effects seen after prenatal and, possibly, postnatal exposure. Thus, effects on adults will be treated separately from effects on developing tissues.

### *9.1.1 Effects on adults*

The effects of methylmercury on adult human beings have been thoroughly described in Environmental Health Criteria 1: Mercury (WHO, 1976b). They will be summarized here with relevant new material added as appropriate.

#### *9.1.1.1 Effects on the nervous system*

The nervous system is the principal target tissue for the effects of methylmercury on adult human beings. The sensory, visual, and auditory functions, together with those of the brain areas, especially the cerebellum, concerned with coordination, are the most common functions to be affected. The earliest effects are non-specific symptoms, such as complaints of paraesthesia, malaise, and blurred vision. Subsequently, signs appear such as concentric constriction of the visual field, deafness, dysarthria, and ataxia. In the worst cases, the patient may go into a coma and ultimately die. In less severe cases, some degree of recovery in each symptom occurs; this is believed to be a functional recovery that depends on the compensatory function of the central nervous system. The subjective complaint of paraesthesia was found to be a permanent symptom in patients exposed in the Japanese outbreak, whereas in the Iraqi outbreak, paraesthesia was transient in many cases. The reason for this difference is not known.

At high doses, methylmercury affects the peripheral nervous system (Rustam et al., 1975). In Iraq, patients had symptoms of neuromuscular weakness that could be

ameliorated by treatment with acetylcholinesterase inhibitors.

Methylmercury poisoning has several important features:

- a long latent period usually lasting several months;
- damage almost exclusively limited to the nervous system, especially the central nervous system;
- areas of damage to the brain are highly localized (focal), e.g., in the visual cortex and the granular layer of the cerebellum, especially in the infolded regions (sulci);
- effects in severe cases are irreversible due to destruction of neuronal cells;
- the earliest effects are non-specific subjective complaints, such as paraesthesia, blurred vision, and malaise.

#### 9.1.1.2 *Effects on non-nervous tissue*

The only effect on human beings not involving the nervous system is the claim that chromosome damage is associated with long-term exposure to methylmercury (Wulf et al., 1986). No further reports have appeared on this subject since the review in Environmental Health Criteria 1: Mercury (WHO, 1976b).

### 9.1.2 *Effects on developing tissues*

#### 9.1.2.1 *Effects on the nervous system*

Observations on both human subjects and animals indicate that the developing central nervous system is more sensitive to damage from methylmercury than the adult nervous system. The first indications arose from the outbreak of methylmercury poisoning in Minamata, Japan, in the 1950s, when it was found that mothers who were slightly poisoned gave birth to infants with severe cerebral palsy. Subsequent studies on experimental animals confirmed the increased sensitivity of the fetus. The Iraqi outbreak in 1971-1972 resulted in cases of severe damage to the central nervous system in infants prenatally exposed. More

recent follow-up studies in Iraq indicated a milder syndrome at lower dose levels (Marsh et al., 1980). In fact, it has been possible to demonstrate a relationship between the maximum hair level in the mothers during pregnancy and the frequency of abnormalities in their infants (Marsh et al., 1981).

The clinical picture is dose dependent. In those infants who have been exposed to high maternal blood levels of methylmercury, the picture is of cerebral palsy indistinguishable from that caused by other factors. Microcephaly, hyperreflexia, and gross motor and mental impairment, sometimes associated with blindness or deafness, is the main pattern (for review, see WHO, 1976b). Milder degrees of the affliction are not easy to diagnose during the first few months of life, but they later become clear. Patients show mainly psychomotor impairment and persistence of pathological reflexes (Marsh et al., 1977, 1980, 1981; McKeown-Eyssen et al., 1983). Milder cases have findings quite similar to the findings in the minimal brain damage syndrome.

Post-mortem observations in Japan indicated that damage is generalized throughout the brain in the case of prenatal exposure, in contrast to adult exposure where focal lesions are predominant. The Japanese cases of prenatal poisoning indicated disturbed development in the cytoarchitecture of the brain and the brain size was diminished in severe cases. Similar pathological findings were reported on autopsies of two prenatally exposed Iraqi infants (Choi et al., 1978). The pathological findings in these studies were attributed to incomplete and abnormal migration of neuronal cells to the cerebellar and cerebral cortices (section 9.3.2).

## 9.2 Occupational Exposure

This type of exposure was reviewed in Environmental Health Criteria 1: Mercury (WHO, 1976b). No new information has become available. In fact, occupational exposure results in effects similar to those reviewed in section 9.1 (e.g., Hunter & Russell, 1954).

## 9.3 Mechanisms of Toxicity

Section 9 is concerned with effects on human beings. However, in discussing mechanisms of methylmercury toxicity, animal and other experimental data are used where they throw light on how damage is inflicted on the human organism.

### *9.3.1 The mature organism*

#### *9.3.1.1 Mechanism of selective damage*

The mechanism of selective damage is not well understood. In a review of publications, Syversen (1982) claimed that the selective effects relate to the ability of certain cells in the central nervous system to repair the damage initially inflicted by methylmercury. Thus, those cells capable of repairing injury survive, whereas those cells that lack the facility to repair the damage are the ones that are destroyed. For example, the small granule cells in the cerebellum lack the repair capacity and are the first cells in that area of the brain to succumb. Jacobs et al. (1977) noted that the small neurons in the central nervous system appear to be especially vulnerable. Such cells have very little cytoplasm and only limited protein synthetic machinery to carry out repair. On the other hand, Berlin (1986) has proposed that selective damage results from the inter-neuronal axonal transport of methylmercury. Thus, the sensory centres, e.g., in the visual cortex, are affected because axonal transport is in the afferent direction leading to a local accumulation of methylmercury. The motor systems are relatively unaffected by methylmercury because axonal transport is in the efferent direction leading to removal of mercury from the motor areas.

#### *9.3.1.2 The latent period*

The reason for the long latent period is not understood. The mean latent period ranged from 16 to 38 days in Iraq, and, in many cases, initial symptoms appeared after the cessation of intake of contaminated bread. In the Japanese outbreaks, it was difficult to determine the exact latent period because in many cases the starting

point of intake was unclear. However, in some cases in Japan, a very long latent period (up to several years) was reported (WHO, 1980). Included in these cases were some patients who showed only slight signs and symptoms but who later developed the clinical features of severe poisoning after they had stopped eating the polluted fish. In the same period of time, the other patients showed relative improvement or progression. A latent period of several years may be partially explained by psychogenic overlay, which modifies the symptoms, or by sub-clinical lesions, which may be revealed by the aging factor. However, slow accumulation in the brain of methylmercury (or of inorganic mercury split off from the methylmercury) cannot be the explanation.

#### 9.3.1.3 *Cellular and molecular mechanisms*

Since the publication of Environmental Health Criteria 1: Mercury (WHO, 1976b), numerous studies on the mechanism of action at the cellular and molecular levels have been reported (Clarkson, 1983; Berlin, 1986). Inhibition of protein synthesis in target nerve cells is a well documented effect in animals that appears before the first clinical signs of intoxication (Yoshino et al., 1966; Carmichael et al., 1975; Omata et al., 1980, 1982; Syversen, 1982; Fair et al., 1987). It occurs also *in vitro* before other cellular functions are affected (Nakada et al., 1980; Sarafian et al., 1984).

Verity and his colleagues (Cheung & Verity, 1985; Sarafian & Verity, 1985, 1986) have identified the step in protein synthesis that is most sensitive to methylmercury. The peptide-elongation process can be affected at high levels of methylmercury, but the first stage of synthesis, associated with transfer RNA, may be the most sensitive. It appears that the inhibition of protein synthesis is general; there is no selective inhibition of formation of any special proteins or group of proteins.

The reason for the special sensitivity of protein synthesis to methylmercury is not known. Jacobs et al. (1977) noted that the mammalian ribosome contains 120 sulfhydryl groups, of which about half are exposed and reactive during peptide formation, and that the chain-initiation factor is strongly inhibited by sulfhydryl

reagents, at least in the case of bacteria. They suggested that the sulfhydryl groups of active ribosomes are more vulnerable than those in other proteins, where disulfide bridge formation may predominate. Methylmercury also interferes with lipids (Nakada & Imura, 1983; Ando et al., 1985), myelin (Ganser & Kirschner, 1985), mitochondrial DNA synthesis (Miller et al., 1985), and glutathione peroxidase (Hirota et al., 1980).

Effects on neurotransmitters and receptors (Kobayashi et al., 1979, 1981; Concas et al., 1983), lipids (Macfarlane, 1981; Rebel et al., 1983; Leblanc et al., 1984), adenyl cyclase activity (Spuhler & Prasad, 1980), membrane structure (Kasuya, 1980), and on the integrity of microtubules have been reported in a variety of experimental systems (Araki et al., 1981; Nakada & Imura, 1982; Sager et al., 1981a,b). Methylmercury inhibits amino acid transport in rat brain microvessels at concentrations similar to those known to cause toxicity in humans (Tayarani et al., 1988). Changes in glucose transport across the blood-brain barrier in rats have been observed in the latent period before overt signs of methylmercury intoxication appear (Hargreaves et al., 1986). When given systemically, methylmercury accelerates axonal transport of proteins in the optic nerve (Aschner, 1986). However, when it is given by intra-ocular injection, methylmercury inhibits protein transport along the optic nerve (Aschner et al., 1986). The relevance of the above findings to the pathogenesis of methylmercury poisoning is still a matter of speculation.

Perhaps more firmly established is the connection between muscular weakness seen in severe cases of poisoning in the Iraqi outbreak and the inhibition of acetylcholine transmission at the neuromuscular junction (Von Burg & Landry, 1976; Shamoo et al., 1976; Atchison & Narahashi, 1982; Quandt et al., 1982; Atchison, 1986). The stimulatory action of methylmercury on the miniature endplate potentials of the neuromuscular junction appears to result from the loss of calcium ions from the nerve terminal mitochondria (Levesque & Atchison, 1988).

### 9.3.2 *Developing tissues*

Post-mortem observations derived from the Japanese and Iraqi outbreaks suggested that the severe prenatal effects seen resulted from incomplete and abnormal migration of neuronal cells to the cerebellar and cerebral cortices. In support of their autopsy findings indicating abnormal neuronal migration, Choi et al. (1979) noted that methylmercury inhibited the *in vitro* migration and movement of cultured human cells. Changes in astrocyte membranes and in motility were also observed in cultures when methylmercury was added (Choi & Lapham, 1980). The ability of methylmercury to damage astrocytes *in vitro* was confirmed by findings of decreased DNA synthesis (Choi et al., 1980; Choi & Kim, 1984). The toxic effect on astrocytes may be relevant to the pathological picture, since these cells are believed to play a role in supporting normal neuronal migration in the developing brain (Choi & Lapham, 1976). More recently, Peckham & Choi (1986) showed that methylmercury alters the anionic surface charge on cultured fetal mouse astrocytes. Cell-to-cell recognition processes were found to be affected in aggregates of mouse cerebellar cells (Jacobs et al., 1986). The authors suggested that the mechanism involved depressed synthesis of specific proteins followed by alterations in microtubules.

A second general mechanism by which brain development could be impaired is the inhibition of cell division (Chen et al., 1979; Sager et al., 1982, 1983; Rodier et al., 1984; Slotkin et al., 1985; Howard & Mottet, 1986; Vogel et al., 1986). Inhibition of cell proliferation probably explains the production of cleft palates in rats (Lee et al., 1979; Olson & Massaro, 1980), although this effect has not been seen in humans. Methylmercury is known to inhibit cell division by causing metaphase arrest, similar to that observed with colchicine, presumably by disruption of the mitotic spindle (Onfelt, 1983). Both spindle microtubules (Miura et al., 1978) and cytoplasmic microtubules in cultured rat glioma cells (Imura et al., 1980; Miura & Imura, 1987) and human fibroblasts (Sager et al., 1983) are disrupted by methylmercury. Damage to the microtubule system appears to underly the toxic effects of methylmercury on lymphocytes (Brown et al., 1988). Sager & Matheson

(1988) have shown that disassembly of microtubules precedes changes in other elements. *In vitro* polymerization of microtubules is also inhibited by methylmercury (Abe et al., 1975; Imura et al., 1980; Sager et al., 1983; De Saint-Georges et al., 1984; Miura et al., 1984). The effect on microtubules appears to be selective and does not involve other components of the cytoskeleton (e.g., vimentin or actin filaments) (Sager, 1988). Vogel et al. (1985) suggested that methylmercury binds to free sulfhydryl groups on the ends and on the surface of microtubules.

Sager et al. (1982, 1984) hypothesized that methylmercury might arrest the division of immature neurons at critical stages of brain development. They administered methylmercury to newborn mice at a time when the external granule layer (EGL) of the cerebellar cortex was rapidly dividing. They found fewer granule cells in the treated animals as well as a decrease in the percentage of late mitotic figures. This incomplete mitosis may have been responsible for the decreased cell numbers.

Destruction or arrest of neuron growth during the development of the central nervous system may be an important general mechanism in the pathobiology of prenatal damage (Rodier, 1977). The deranged cell migration reported by Choi et al. (1978) and the arrested cell division found by Sager et al. (1984) might both be an expression of the action of methylmercury on microtubules and thus be consistent with the hypothesis that microtubule protein is an important molecular target for methylmercury in the developing brain.

Enzymes associated with myelin formation have been found to be affected in the early postnatal period in rats (Grundt & Neskovic, 1985). Morphological de-differentiation of cultured brain cells has been shown to occur after addition of methylmercury (Grundt et al., 1981, 1982). These effects occur at lower methylmercury levels than those affecting energy metabolism (Grundt & Bakken, 1986).

Choi et al. (1981) noted incomplete arborization of the dendritic tree of Purkinje cells in mice dosed with methylmercury in the early postnatal period.

### 9.3.3 *Summary*

*In summary, the clinical and epidemiological evidence indicates that prenatal life is more sensitive to the toxic effects of methylmercury than is adult life. The inhibition of protein synthesis is one of the earliest detectable biochemical effects in the adult brain, though the sequence of events leading to overt damage is not yet understood. Methylmercury can also react directly with important receptors in the nervous system, as shown by its effect on the acetylcholine receptor in the peripheral nerves. Concerning prenatal exposure, the effects of methylmercury seem to be quite different and of a much more general basic nature. It affects normal neuronal development and leads to altered brain architecture, heterotopic cells, and decreased brain size. Methylmercury may also be exerting an effect, perhaps through inhibition of the microtubular system, on cell division during critical stages of formation of the central nervous system.*

## 9.4 Dose-Effect and Dose-Response Relationships in Human Beings

The relationships between concentrations in indicator media (e.g., blood and hair) or body burdens and the magnitude of an effect or frequency of an effect (response) were discussed in Environmental Health Criteria 1: Mercury (WHO, 1976b) using data from the Japanese and Iraqi outbreaks. They will be summarized here and considered in conjunction with studies reported subsequently. Other extensive and detailed reviews have been published since 1976 (Tsubaki & Irukayama, 1977; Inskip & Piotrowski, 1985; Tsubaki & Takahashi, 1986).

Prenatal and adult exposures will be treated separately in view of the differences, both qualitative and quantitative, in effects and dose-response relationships.

### 9.4.1 *Adult exposure*

This section will examine new data published since 1976 and include a re-analysis of samples of hair, brain, and other tissues obtained from patients in Minamata and Niigata, Japan, the clinical follow-up of individuals exposed to methylmercury in Niigata, a new analysis of the

Iraqi data, and reports on high fish consumers in Canada and elsewhere.

9.4.1.1 *The Minamata and Niigata outbreaks*

Many of the original samples collected in Minamata and Niigata, Japan, had been analysed by the dithizone procedure. Previous risk estimates were based on blood and hair mercury levels measured by this procedure. Tsubaki et al. (1978) reported on the repeat analysis of a hair sample from the patient in Niigata with the lowest hair mercury concentration at the onset of symptoms (52 μg/g). Re-analysis by atomic absorption yielded a value of 82.6 μg/g. Other hair samples collected from Niigata yielded values of about 100 μg/g for the onset of symptoms. As for blood samples, none were available for re-analysis by atomic absorption. The patient with the lowest blood level had a concentration of just below 200 μg/litre when extrapolated to time of onset of symptoms. However, the extrapolation used in Environmental Health Criteria 1: Mercury (WHO, 1976b) was based on a few points only, and the statistical uncertainty in the extrapolated value was high. Furthermore, the hair samples from the same patient indicated that the blood concentration was probably higher. Other blood samples extrapolated to values above 300 μg/litre. Further evidence by Tsubaki et al. (1978) indicates that hair and blood mercury levels at the onset of symptoms may not have been the true maximum values in these patients. Analyses of hair samples from Niigata indicate that the mercury concentrations may have attained peak values about 2 months before the onset of symptoms. A stringent government warning against the consumption of contaminated fish was issued by June 1965; in many patients, symptoms appeared about 2 months later (WHO, 1980).

Such evidence indicates that previous evaluations of the earlier data from Niigata may have underestimated the blood and hair concentrations associated with poisoning in the most sensitive patient and, therefore, overestimated the risk of poisoning. However, it should be noted that the atomic absorption method does need not always yield higher results than the dithizone method. Tsubaki et al. (1978) quote data from two hair samples in which agreement between the two results was excellent. Furthermore, the

brain and other tissues were preserved for many years before the atomic absorption measurements were made (1973), whereas the dithizone method was used on fresh tissue (1956-1960).

Information from the clinical follow-up from Niigata (Tsubaki & Irukayama, 1977; Tsubaki et al., 1978) suggests that there may be a latent period of several years between peak mercury concentrations and onset of symptoms. Such a latent period was reported in four patients whose maximum hair concentrations were in the range of 50-300 mg/kg, as measured by atomic absorption (Tsubaki et al., 1978). The results of studies on primates indicate latent periods of up to 1 year under conditions of continuous exposure. These latent periods are apparently dose dependent in animals (Evans et al., 1977). A relationship between length of latent period and maximum hair concentrations was not apparent in the few Niigata cases. The delayed cases were mild, showing non-specific symptoms, so that cases of methylmercury poisoning could not be diagnosed with complete certainty. Follow-up studies examining mortality patterns in the Minamata population, including both poisoning cases and controls, did not reveal any clear pattern of mercury-related deaths (Tamashiro et al., 1984, 1986, 1987).

#### 9.4.1.2 *The Iraqi outbreak*

This outbreak of mass poisoning took place in the winter of 1971-1972 (Bakir et al., 1973; Kazantzis et al., 1976a,b; Al-Mufti et al., 1976; Greenwood, 1985). Seed grain treated with a methylmercury fungicide was used to prepare homemade bread in rural communities throughout the country. Consumption probably began in October-November, 1971, and the first cases of severe poisoning were admitted to hospital at the end of December, 1971. Total hospital admissions rose to just over 6000, with most of these occurring in January, 1972. Over 400 deaths attributed to methylmercury were recorded in hospital. Both sexes and all ages were affected. Individual exposure ranged from a low non-toxic intake (when a few contaminated loaves were consumed) to prolonged daily intake (1-2 months), which in some cases produced severe signs of poisoning. The first effects were complaints of paraesthesia or

malaise, followed by signs of ataxia, constriction of visual fields, and hearing loss. Some people experienced muscular weakness, which improved after treatment with an acetylcholinesterase inhibitor. Changes in peripheral nerve velocity were recorded in some severe cases. However, most of the signs and symptoms were attributed to damage to the central nervous system. Effects on non-nervous tissue appeared to be absent or negligible.

Early in the outbreak, it was noted that some prenatally exposed infants showed signs of severe cerebral palsy similar to the cases reported in the Minamata outbreak (Amin-Zaki et al., 1974). Later, more subtle effects on the developing nervous system were detected (Marsh et al., 1980). Fig. 2, reproduced from Environmental Health Criteria 1: Mercury (WHO, 1976b), demonstrates both dose-effect and dose-response relationships. For any given sign or symptom, e.g., paraesthesia, there is a background frequency indicated by the line parallel to the horizontal axis. Two scales are given for the horizontal axis because two different methods were used to estimate the maximum body burden. At higher values of the body burden, the frequency of response rises in proportion to the logarithm of the body burden (the horizontal axis has a logarithmic scale). The two lines (the horizontal and sloped line) form the shape of a "hockey stick", and this type of dose-response analysis is referred to by this name.

The body burden corresponding to the point of intersection of the two lines in the "hockey stick" was referred to as a "practical threshold" by the authors (Bakir et al., 1973). This threshold increases with increasing severity of the effects. Thus, using the upper scale in Fig. 2, the threshold for paraesthesia occurs at a body burden of about 25 mg, for ataxia at about 50 mg, for dysarthria at about 90 mg, for hearing loss at about 180 mg, and for death at over 200 mg.

The dose-response relationship is illustrated by the "hockey-stick" line for each sign and symptom. Thus, the increase in frequency of paraesthesia increases in proportion to the log of the maximum body burden above the practical threshold. This increase is assumed to be caused by methylmercury. In fact, the only proof that methylmercury produced certain effects in this population is that:

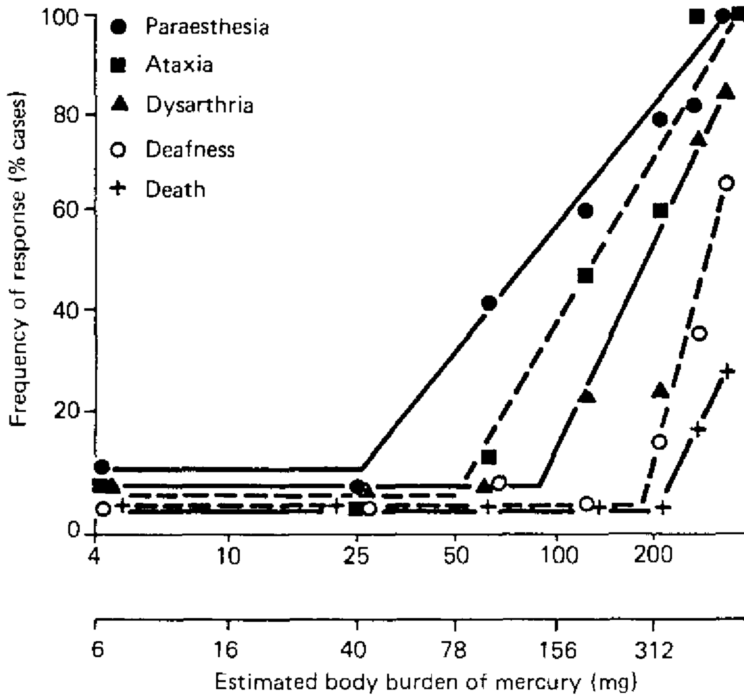


Fig. 2. The relationship between frequency of signs and symptoms and the estimated body burden of methylmercury. From: Bakir et al., 1973.
Both scales of the abscissa refer to body burden of methylmercury at the cessation of exposure. The two scales represent different methods of calculating the body burden as discussed in Environmental Health Criteria 1: Mercury (WHO, 1976b).

(a) these effects followed a known high exposure to methylmercury; (b) the frequency and severity of these effects increased with increasing exposure to methylmercury; (c) these effects are similar to those seen in other outbreaks of methylmercury poisoning; and (d) the major signs have been reproduced in some animal models.

This cause-effect relationship is most difficult to establish at body burdens close to threshold levels. Here, the only effect may be the patient's complaint of paraesthesia. This is a non-specific end-point that has a variety of causes other than methylmercury. The overall conclusion depends on a group-based statistical association between paraesthesia and exposure to methylmercury. Fig. 2 shows that the practical threshold value for paraesthesia is a body burden of 25-40 mg mercury. Using the metabolic model discussed in section 6, the body burden of 25-40 mg mercury is equivalent to a blood level of 250-400 µg/litre. This range of blood values compares favourably with the lowest-observed-effect level in Niigata. The "hockey-stick" analysis depicted in Fig. 2 implies the existence of a population threshold for the neurological effects of methylmercury in adults. Though the true population threshold cannot be determined, "the practical threshold" serves as an estimate of the population threshold.

A re-analysis of Iraqi data has been published by Nordberg & Strangert (1976, 1978, 1982). This analysis assumed a continuous distribution of individual thresholds superimposed on a background frequency for such symptoms as paraesthesia. The analysis also took into account the inter-individual variation in whole-body biological half-times. The half-time was used together with other parameters of the metabolic model for methylmercury to estimate blood concentrations that would result from long-term daily intake of methylmercury. In turn, the blood levels can be related to the maximum body burdens by the distribution parameters presented in section 6. Thus, these two distributions of thresholds and biological half-times were combined to give an overall estimate of the risk of paraesthesia for a given steady-state daily intake of methylmercury. The results are presented in Fig. 3. The calculations indicate that an intake of 50 µg/day in an adult would involve a risk of about 0.3% of the symptoms of paraesthesia, whereas an intake of 200 µg/day would involve a risk of about 8%. As pointed out by Nordberg & Strangert (1976, 1978, 1982), the background frequency of these non-specific symptoms, such as paraesthesia, plays a key role in determining the accuracy of the estimates of response of low frequencies. From the same Iraqi data, the authors

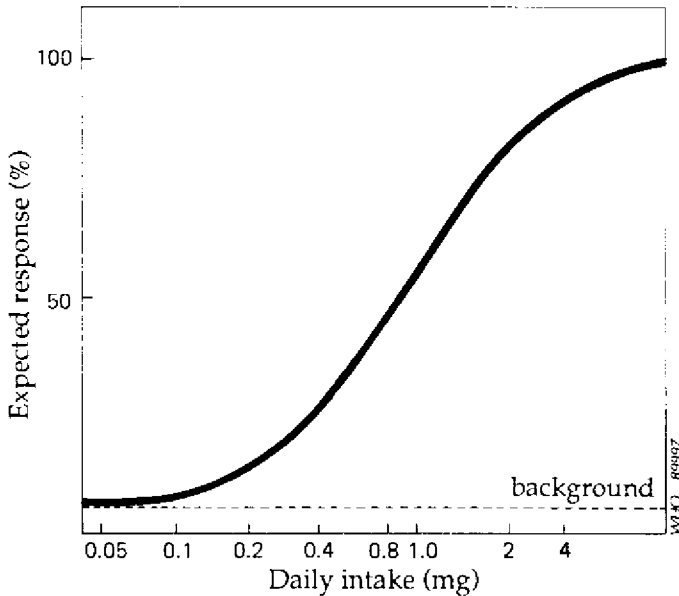


Fig. 3. The calculated relationship between frequency of paraesthesia in adults and long-term average daily intake of methylmercury. From: KHM (1981).
The broken line is the estimated background frequency of paraesthesia in the population.

estimated the background frequency of paraesthesia to be 6.3%. However, there is considerable uncertainty in determining the precise value of the background frequency, and this uncertainty becomes the dominant cause of error at low rates of exposure.

The re-analysis by Nordberg & Strangert is in agreement with the conclusions of Environmental Health Criteria 1: Mercury (WHO, 1976b) that the prevalence of the earliest effects could be expected to be approximately 5% in the adult population following a long-term daily methylmercury intake of 3-7 μg mercury/kg body weight. Such a long-term daily intake should give rise to blood concentrations of approximately 200 μg mercury/litre and maximum hair concentrations of about 50 μg mercury/g. It

should be noted that estimates of the frequency of paraesthesia below daily intakes of about 200 μg are extrapolations beyond the observed data and assume the absence of a population threshold.

#### 9.4.1.3 *Exposed populations in Canada*

More recently, clinical and epidemiological assessments have become available from studies of Canadian Indian population groups exposed seasonally over a long period of time to methylmercury through fish consumption. The levels of exposure, as determined by the analysis of blood and hair samples (or both), were generally lower than those in the diagnosed cases of poisoning studied in Iraq and in the Niigata epidemic in Japan. The highest blood level of mercury recorded in Canada was 660 μg/litre (Wheatly, 1979).

Harada et al. (1976) clinically examined 89 residents of two Indian reservations who had been exposed to methylmercury by ingestion of contaminated fish. They found a number of signs and symptoms that have been associated with methylmercury intoxication. However, as the authors pointed out, the signs and symptoms were relatively mild and many of them were thought to be due to other factors. In the absence of controls, it is difficult to evaluate the possible role of methylmercury in the clinical findings reported in this study.

A report of the Medical Services Branch of the Department of National Health and Welfare, Canada, recorded the clinical examination of 84 subjects who had a history of blood mercury levels above 100 μg/litre (Wheatley, 1979). Mild symptoms and signs were found that could be attributed to possible methylmercury exposure, but the causal relationship between exposure and effects was uncertain. However, of the 84 subjects examined, 11 cases were found where such an association could not be excluded.

A major epidemiological study was carried out on Cree Indians from northwestern Quebec, Canada, exposed to methylmercury in fish (McKeown-Eyssen & Ruedy, 1983a,b). The authors claimed to find an association in adult men and women between a set of neurological abnormalities and

the estimated exposure to methylmercury. However, it should be pointed out that this association was seen by only four of seven observers who reviewed videotaped recordings of the neurological screening tests. The severity of these neurological abnormalities is described as mild or questionable. It was not possible to estimate any threshold body burden or hair levels because this population had been exposed possibly for most of their lives and, therefore, peak values in previous years were unknown. However, observations on this population over several years indicated maximum blood concentrations below 600 μg/litre. On examining the reports from these studies, a WHO expert group (WHO, 1980) pointed to the potential importance of the long duration of exposure in the Canadian Indians and raised the possibility that this might be the first example of an endemic disease due to exposure to methylmercury.

#### 9.4.1.4 Other fish-eating populations

In addition to the extensive Canadian studies mentioned above, some other reports have been published since 1976 on the blood or hair mercury levels in populations exposed to methylmercury through fish (Bacci et al., 1976; WHO, 1976b; Riolfatti, 1977 ; Haxton et al., 1979; Turner et al., 1980; Valciukas et al., 1986). Taking all reports into consideration, it seems that about 100 adults, who were exposed to methylmercury in fish, have been identified outside Japan or Iraq as having had blood levels above 200 μg/litre. In none of these cases has a diagnosis of Minamata disease been made, but it is possible that some may have suffered mild methylmercury poisoning. Even if it is assumed that none of these people suffered any adverse effects from the exposure, such a negative finding is still consistent (95% confidence level) with the maximum risk for paraesthesia of about 3%.

#### 9.4.1.5 Special groups

The above-mentioned risk estimates may not apply to pregnant women. Some severe cases of poisoning among pregnant women exposed to high doses were reported in Iraq (WHO, 1980). At lower doses, transient paraesthesia and other mild symptoms have been reported (Tsubaki &

Irukayama, 1977; Marsh et al., 1977, 1980, 1981). Maternal paraesthesia coincided with peak hair concentrations of methylmercury (Marsh et al., 1987). These observations suggest a greater risk for pregnant women than for non-pregnant women.

#### 9.4.1.6 *Summary*

*The overall conclusion is that the reported relationships between response and body burden, hair, or blood mercury concentrations are essentially the same as those reported in Environmental Health Criteria 1: Mercury (WHO, 1976b). It is possible that the latent period after cessation of exposure may extend to one year or thereabouts. Pregnant women may exhibit paraesthesia at lower methylmercury exposure levels than non-pregnant women, suggesting a greater risk for pregnant women.*

### 9.4.2 *Prenatal exposure*

In contrast to the adult exposure situation, a considerable amount of new data has been published on dose-response relationships for human prenatal exposure. In 1976, when Environmental Health Criteria 1: Mercury (WHO, 1976b) was published, it was known that prenatal exposure could cause fetotoxic effects in human beings. In the Minamata outbreak, 23 children believed to be exposed *in utero* had severe cerebral involvement (palsy and retardation), whereas their mothers had mild manifestations or none at all (Takeuchi, 1977). Mercury levels in the mothers during pregnancy were not recorded (WHO, 1976b). There were no reports of prenatal poisonings in the Niigata outbreak. Psychological studies carried out in the Minamata area with children from elementary schools and junior high schools did not reveal major defects of IQ, compared with children from a control area (Harada & Moriyama, 1977). However, data on maternal exposure were not available. In another study from Minamata there was a correlation between mercury levels in umbilical blood and the occurrence of mental retardation in children (Harada et al., 1977).

Studies of prenatal exposure to methylmercury based on populations in Canada, Iraq, and New Zealand have now been published.

9.4.2.1 *Iraq*

Since the publication of WHO (1976b), results have been obtained from a clinical follow-up study on 29 infant-mother pairs in Iraq (Marsh et al., 1977, 1980). These reports described psychomotor retardation in infants caused by prenatal exposure (social bias excluded). A relationship was noted between maximum hair concentrations, measured in 1-cm segments during pregnancy, and the frequency of neurological effects in the infants. These effects included delayed achievement of developmental milestones with or without neurological signs. The infants were 4½-5 years of age at the time of last examination.

At hair mercury levels below 180 mg/kg, the infants showed minimal clinical neurological signs, but there was clear evidence of effects on psychomotor function, such as delayed walking or talking (Marsh et al., 1977). The following criteria were adopted for developmental abnormalities:

> "motor retardation if the child was not walking at 18 months, speech retardation if not talking by 24 months, mental retardation or seizures (or convulsive-like attacks) according to the history provided by the mother, and neurological signs by agreement of the two examiners. No standards are available for head circumference or height of Iraqi children, so these factors were evaluated in terms of standard deviations below the mean for the group".

Subsequently, a more complete report (Marsh et al., 1981) became available on 84 infant-mother pairs, including the 29 pairs described above. The peak maternal hair levels ranged from 0.4 to 640 mg/kg. Severe neurological deficits were observed in five children. These severe effects are illustrated by the case report of one of these children. At the age of 4 years and 9 months, the child was blind and deaf and was unable to stand, walk, or talk. Tonic neck responses were present. All limbs showed an increase in tone and deep tendon reflexes with extensor

plantar responses and abnormal posture of the wrist. Microcephaly was present, with a head circumference of 43 cm. The boy's height was 98 cm (Marsh et al., 1977).

These severely affected children had been exposed to peak maternal levels during the second trimester of pregnancy. These findings agree with a histopathological report of Choi et al. (1978), who found evidence of abnormal neuronal migration in the brain of Iraqi victims exposed maximally in the third and fourth months of pregnancy. This is known to be the critical period for neuronal migration (Sidman & Rakic, 1973).

These reports (Marsh et al., 1977, 1981) were based on the analysis of 1-cm segments of hair bundles. Peak hair concentrations probably underestimated the actual peak blood concentrations due to misalignment of hair strands during collection and to the differences in growth rates of individual strands (for further discussion, see Giovanoli-Jakubczak & Berg, 1974). Furthermore, the analytical methods used in the hair analysis had a recovery of 73 ± 10% (Wigfield et al., 1981).

Analysis of these Iraqi hair samples has been repeated using single-strand sampling and X-ray fluorescence giving complete recovery (Jaklevic et al., 1978). Detailed results from the Iraqi outbreak have been reported by Marsh et al. (1987) are given in the Appendix. The effects in mothers during pregnancy were mild and transient, the most frequent symptom being paraesthesia. Symptoms were reported by the mother more frequently as exposure level increased. The severity of effects in the mother was much less than that in her offspring. Two of the mothers of the four most severely affected infants (pair numbers 45, 56, 68, and 70) recalled no symptoms, and the others complained only of transient paraesthesia during pregnancy. This confirmed the findings of Harada (1968) on infant-mother pairs in the Minamata outbreak.

According to Marsh et al. (1987), the physical examination of the children included:

> "observation, measurement of head circumference and body length, cranial nerve signs, speech, involuntary movements, strength, deep tendon reflexes, plantar

responses, coordination, dexterity, primitive reflexes, sensation, posture, and ability to sit, stand, walk, and run. A scoring system was adopted. When the neurological examination result was absolutely normal, the score was 0. In attempting to identify minimal signs, points were awarded for borderline findings such as possibly increased reflexes. Scores of 0-3 indicated no definite abnormality. The highest score in the most severely affected child was 11. The neurological score was limited to signs found on examination, and points were not awarded for features of retardation reported by the mother".

Four cases received a neurological score of 11. The evidence is strong that these were severe cases of prenatal methylmercury poisoning. The lowest-observed maximum maternal hair level for these severe cases was 404 mg mercury/kg (mother-infant pair number 56). However, none of these observed symptoms were specific to prenatal methylmercury poisoning. The possibility of confounding factors was considered by the authors:

"Maternal alcohol consumption was not a problem. They followed the Moslem precept to avoid alcohol, so the fetal alcohol syndrome was not a consideration. None of them smoked. The absence of antenatal medical supervision was uniform, so that no prescription medication were taken and non-prescription medications were rarely available. There were no drug-induced fetotoxic effects to account for. These were agricultural communities with little socio-economic variation and no evidence of malnutrition".

The evidence that such non-specific symptoms were caused by methylmercury is based on a statistical correlation of the frequency of these symptoms with methylmercury exposure and the absence of confounding factors. This was the first report of a milder syndrome of prenatal methylmercury poisoning, as opposed to the severe cases discussed above.

An example of one such statistical correlation is given in Fig. 4. The frequency of a symptom of motor retardation (delayed onset of walking) is plotted against the logarithm of the maximum maternal hair concentration

during pregnancy. The continuous line in Fig. 4a gives the best fit to the data calculated according to a non-parametric model. The frequency of response increases smoothly from virtually zero at a maternal hair mercury level of 5 mg/kg to approximately 70% at the highest concentration. The shaded area is made up of individual 95% confidence limits for the individual response frequencies. The narrow confidence limits at the lowest hair levels (about 1 mg/kg) indicate a low background response frequency of less than 5%. Marsh et al. (1987) noted that, in five European countries, 10% of infants were not walking by the age of 16 months and 5% of a sample of infants in Paris, France, were not walking by 18 months, this being the criterium used in their study.

Fig. 4. The relationship between the maximal maternal hair concentrations during pregnancy and the frequency of cases of motor retardation in offspring. Calculated from data in the Appendix according to the method of Cox et al. (1989).

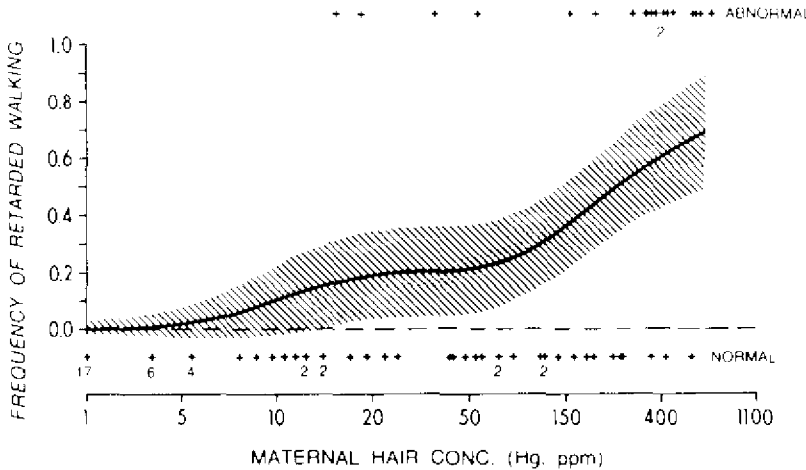


Fig. 4a. A non-parametric kernel smoothing analysis (a form of forward moving average) of the relationship between maximal maternal hair concentration of methylmercury during pregnancy and retarded walking in the offspring. The shaded area denotes non-simultaneous 95% confidence limits for the smooth curve. Normal and abnormal outcomes are plotted below and above, respectively, according to the corresponding maternal hair value.

The non-parametric 95% confidence limits are superimposed on two parametric models (the "hockey-stick" and logit models) in Fig. 4b. The figure shows that both parametric models are consistent with the data and with each other. The two curves are close to each other and both lie entirely within the non-parametric confidence limits.

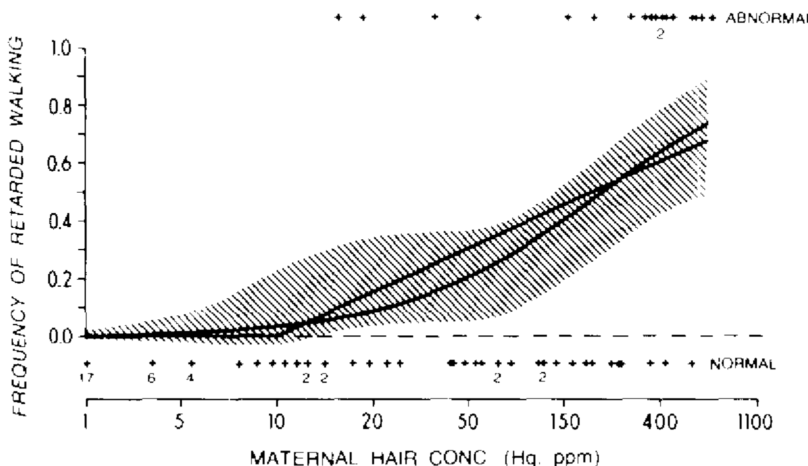


Fig. 4b. Plots of the logit and "hockey-stick" parametric models of dose-response between retarded walking and maximum maternal hair concentrations during pregnancy. The two dose-response curves are shown by solid lines. The shaded area represents the 95% confidence limits by kernel smoothing.

The collection of non-simultaneous confidence intervals, as depicted in the shaded area, cannot be used to obtain confidence intervals for such parameters as hair concentration for a 10% or 50% risk. Instead, the parametric models were used. The result for the hockey-stick model are given in Table 10.

The best estimate of a predicted threshold with the hockey-stick model is a maximum maternal hair concentration during pregnancy of 7.3 μg mercury/g with an upper confidence limit of 13.6 μg mercury/g. This best

Table 10. The dependence of "practical" threshold values of hair mercury concentration and upper confidence limits on background frequency of responses[a]

| Response | Background (%) | "Hockey-stick" model | |
|---|---|---|---|
| | | Practical threshold (mg mercury/kg) | Upper 95% limit (best fit) |
| Retarded walking | 0[b] | 7.3 | 13.6 |
| | 2[c] | 8 | 17 |
| | 4[c] | 9 | 190 |
| | 8[c] | 119 | 230 |
| Central nervous system signs | 2[c] | 7.8 | 24 |
| | 4[c] | 8.4 | 32 |
| | 9[b] | 10 | 287 |

[a] Data in Appendix according to Cox et al. (1989).
[b] The best fit of the background frequency from data.
[c] Assumed background frequency.

fit corresponds to a background of zero. This probably is the outcome of the small number of infant-mother pairs in the low exposure region. An assumed background frequency of 2% or 4% does not greatly change the estimated predicted threshold values (8 and 9%, respectively). However, an assumed background of 4% greatly increases the upper 95% confidence limit, and an assumed background of 8% dramatically increases the estimate of the threshold to 119 μg mercury/g. These changes with increased values for the background frequency are due in part to the distribution of the data (the four abnormal values in the hair mercury concentration range from 10 to 50 μg/g) and in part to the assumed higher background values being further away from the best fit (0%).

However, a population threshold might not exist and the hockey-stick model will not then be applicable to these data. Thus the assumption that there is zero risk at the threshold value estimated by the hockey-stick model would be in error. The logit model provides a continuous relationship between dose and response and will therefore give an estimate of the error in assuming zero risk at the threshold dose estimated by the hockey-stick model. Thus according to logit analysis, the excess risk over

background is 5% at the threshold hair mercury level of 7.3 mg/g determined by the hockey-stick model. In short, if the hockey-stick model is not applicable, the estimated threshold of 7.3 mg/g will underestimate the risk by 5% (Fig. 4b).

The logit model, in agreement with the hockey-stick model, gives a background frequency value of 0% according to best fit of the data.

The logit and hockey-stick curves for abnormal central nervous system signs are depicted in Fig 5. The curves are superimposed on the 95% confidence limits estimated non-parametrically as described for Fig. 4.

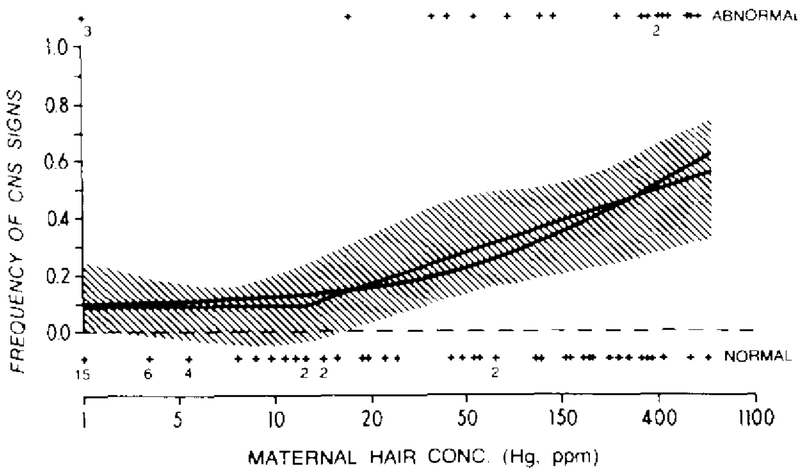


Fig.5. Plots of the logit and "hockey-stick" parametric models of dose-response between central nervous system signs and maximum maternal hair concentrations during pregnancy. The two dose-response curves are shown by solid lines. The shaded area represents the 95% confidence limits by kernel smoothing. Calculated from data in Appendix according to the method of Cox et al. (1989).

The two parametric models are consistent with each other and with the non-parametric confidence limits. With

all three models, a statistically significant dose-response relationship exists.

The hockey-stick model gives the best estimates of the practical threshold at 10 μg mercury/g but with a very high confidence limit (287 μg mercury/g) (Table 10).

Lower assumed values of the background frequency (2% and 4%) give roughly the same practical threshold value, but with lower upper confidence limits (24 and 32 μg mercury/g, respectively). The lower upper limit values are due to the fact that a definite assumed value for the background frequency was used, whereas 9% is the best-fit estimate of background and consequently the overall uncertainty is greater.

The logit model estimates a similar background frequency (9.3%). The excess risk over background is about 5% (Fig. 4).

Thus, the data in the Appendix can be used to demonstrate a statistically significant dose-response relationship for signs and symptoms of prenatal poisoning. Estimates of a "threshold" or highest no-effect concentration were made with the hockey-stick model. These estimates are subject to considerable uncertainty due to the small number of infant-mother pairs. As in the adult dose-response relationships (see Fig. 3 and section 9.4.1.2), the background frequency can greatly influence estimates of risk at low (close to background) response rates, yet cannot be estimated accurately due to the small number of data points at the lowest hair mercury levels.

#### 9.4.2.2 Canada

McKeown-Eyssen et al. (1983) examined the relationship between prenatal exposure to methylmercury and neurological and developmental abnormalities among 234 Cree Indian children aged 12-30 months from four communities in northern Quebec, Canada. The authors described their study as follows:

> "A medical team visited each community and examined 95% of the eligible children and their mothers, 'blinded' to their methylmercury exposure. One of the four pediatric neurologists documented each child's

height, weight, and head circumference, assessed dysmorphic and congenital features, and reported the presence or absence of acquired disease. A neurological examination was also conducted and included an assessment of special senses, cranial nerves, sensory function, muscle tone, stretch reflexes, coordination, and persistence of the Babinski response which was judged to be abnormal for the child's age, as well as a summary of the presence or absence of neurological abnormality. Finally, the neurologist assessed the child's development by use of the Denver developmental scale; for each child, the results were expressed as the percentage of total test items that were passed, separately for gross and fine motor development, language development, and personal/social skills.

"Each mother was interviewed about her alcohol and tobacco consumption both during the relevant pregnancy and at the time of the interview. Because of the uncertainty about the accuracy of the reporting, women were classified simply as users of alcohol or abstainers, and as smokers or nonsmokers according to whether they reported ever drinking or smoking. Caffeine intake was calculated from answers to questions on tea and coffee consumption.

"Information on pregnancy, labour, and delivery were sought from the medical certificate of childbirth, a standard form that reports the major characteristics of pregnancy and delivery for all births in Quebec. Because some deliveries occurred in the bush, these certificates could be obtained for only 85% of the births.

"Methylmercury concentrations of the hair were measured in alternate one centimeter segments, beginning with the scalp-end segment. The maximum concentration in the segment of hair corresponding to the period from one month before conception to one month after delivery was used as an index of prenatal exposure.

"A search was conducted to establish which measures (if any) of neurologic function and development were associated with methylmercury exposure. This was achieved by use of a regression analysis of the

relationship between the methylmercury exposure index and the results of four tests of neurologic function (coordination, cranial nerves, muscle tone or reflexes, and an overall neurologic assessment) and measures of four aspects of the Denver developmental scale (gross and fine motor development, language development, and personal/social skills). Once the measure of neurologic function most closely associated with exposure was identified, the odds ratio was estimated from a discriminant analysis in which children were classified as cases or controls depending on the presence or absence of abnormality of the relevant neurologic function. The analysis distinguished between the cases and controls first on the basis of confounding variables potentially associated with the neurologic abnormality (child's age, duration of breast-feeding, mother's age, and mother's smoking habit and consumption of beverages containing alcohol and caffeine), and then on the basis of the prenatal indices of methylmercury exposure".

The ages of the mothers covered a wide range: 13% were below 20 years of age and 15% were at least 35 years old. About two-thirds said they consumed alcohol and slightly more were smokers. The percentages of high risk pregnancies, complications at delivery, and duration of breast feeding were similar for boys and girls. The birth weight of the children tended to be above normal (34% weighed over 4 kg).

The mean index of mercury exposure (maximum maternal hair concentration during pregnancy) was the same (6 μg/g), for both boys and girls, and only 6% of values were above 20 μg/g. None of the children showed abnormal physical development, but "abnormality" of muscle tone or reflexes was positively associated with the prenatal index of methylmercury exposure ($P < 0.05$, 2-tailed). The highest maternal hair level in this study group of 97 males was 23.9 μg/g (Table 10). No other measure of neurological function or development was significantly associated with methylmercury exposure either before or after adjustment for confounding variables. In girls, no adverse effects were associated with mercury exposure. In fact, a negative association was found between one neurological abnormality (incoordination) and prenatal mercury

exposure. McKeown-Eyssen et al. (1983) expressed some reasons to doubt the "importance" of the finding of methylmercury effects in boys. They noted that the "abnormality of muscle tone or reflexes . . . was . . . of doubtful clinical importance", that previously reported prenatal effects were at higher exposures, that a consistent dose-response relationship was not seen in the boys (Table 11), and that the effect was only seen in boys and not in girls. Consequently, in their interpretation of the data, the authors did not exclude the possibility that the positive findings were chance observations.

Table 11. Prevalence of abnormality of muscle tone or reflexes according to maternal mercury levels during pregnancy[a]

| Prenatal exposure[b] index (mg/kg) | Number of boys | % abnormal |
|---|---|---|
| 0 - 1.9 | 19 | 15.8 |
| 2 - 2.9 | 18 | 5.6 |
| 3 - 4.9 | 19 | 26.3 |
| 5 - 6.9 | 14 | 0 |
| 7 - 12.9 | 14 | 7.1 |
| 13 - 23.9 | 13 | 38.5 |
| Total | 97 | 15.5 |

[a] Adapted from: McKeown-Eyssen et al. (1983).
[b] Maximum maternal hair concentration during pregnancy.

### 9.4.2.3 *New Zealand*

Kjellstrom et al. (1986) reported preliminary tests carried out on prenatally exposed children in a fish-eating group in New Zealand. The study started with a cohort of 11 000 recent mothers and their offspring. Approximately 1000 of these mothers reported that they had consumed fish more than three times per week during pregnancy. Analysis of samples of maternal head hair revealed that 73 of the mothers had levels above 6 mg/kg. People of Pacific Island descent accounted for 62%, Maoris for 27%, and Europeans 11% of this group of 73.

Only 31 offspring from this group of 73 mothers could be contacted by the time they were 4 years old. They were matched according to ethnic group, maternal age, birthplace, and birth date with offspring having low prenatal exposure to methylmercury (maternal hair mercury below 6 mg/kg). The Denver Development Test, carried out on a double-blind basis, was used to assess the effects of methylmercury. Abnormal or questionable results were found in 17% of the controls, compared with 50% in the children exposed to high mercury levels (maternal hair mercury levels above 6 mg/kg). The difference was statistically significant.

A statistically significant dose-response relationship was found between mean maternal hair mercury levels during pregnancy and the frequency of deficient Denver Test results. No influence of socio-economic factors (based on place of residence), maternal health status, or smoking habits was seen. However, other confounding factors inherent in these studies make it difficult to draw final conclusions.

In 1985, it was possible to locate 61 of the original 73 high-exposure children and to conduct detailed psychological and scholastic tests (carried out on a double-blind basis) at the age of 6-7 years (Kjellstrom et al., 1989). At this stage, the children had completed at least one year at school. These tests included, among others, the revised Wechsler Intelligence Scale for Children (WISC-R) and the Test of Language Development (TOLD).

The high-exposure children (maternal hair mercury levels within the range of 6-86 mg/kg, with the second highest value being 19.6 mg/kg) were compared with three matched groups: one group with maternal hair mercury levels of 3-6 mg/kg and two groups with levels below 3 mg/kg (one group with high fish consumption and one with low fish consumption). The mothers were matched for child's sex and maternal ethnic group, age, smoking habits, residence area, and residence time in New Zealand.

The results of the different tests were correlated, and showed that individual children with low scores in the TOLD or WISC-R tests also had low scores in the other tests. For those children who had been tested both at age

4 (Kjellstrom et al., 1986) and at age 6-7 (Kjellstrom et al., 1989), there was also a correlation between the Denver Test and the IQ scores (WISC-R scale). The subgroups were small, but the data indicated that a child who had poor Denver Test results was highly likely to score very poorly in the IQ test at school age. According to the authors' summary, although "methylmercury exposure contributes only a small part of the variation in tests results" and "results of the psychological test variables are influenced by the child's ethnic background", the study suggests that "an average hair mercury level during pregnancy of 13-15 mg/kg (equivalent to about 25 mg/kg peak mercury level) may be associated with a decreased test performance" (Kjellstrom et al., 1989).

It should be noted that the studies in Canada and Iraq used maximum maternal hair concentrations during pregnancy based on 1-cm segments (roughly one month's hair growth). Kjellstrom et al. (1986, 1989) state that their mean maternal hair values should be multiplied by a factor of 1.5 to obtain the maximum 1-cm value during pregnancy.

#### 9.4.2.4 *Summary*

*Severe derangement of the developing central nervous system can be caused by prenatal exposure to methylmercury. The lowest level (maximum maternal hair mercury concentration during pregnancy) at which severe effects were observed was 404 µg/g in the Iraqi outbreak. The highest no-observed-effect-level (NOEL) for severe effect was 399 µg/g. Fish-eating populations in Canada and New Zealand have also been studied for prenatal effects, but exposure levels were far below the highest NOEL for severe effects in Iraq and no severe effects were seen.*

*Evidence of psychomotor retardation (delayed achievement of developmental milestones, a history of seizures, abnormal reflexes) were seen in the Iraqi population at maternal hair levels well below those associated with severe effects. A statistical analysis revealed that one of these effects (motor retardation) rose above the background frequency at maternal hair mercury levels (maximum level during pregnancy) of 10-20 µg/g. This range of values in maternal hair is consistent with all available evidence and can be accepted as the range of critical concentrations. The Canadian study found that maternal hair levels were positively associated with*

*abnormal muscle tone or reflexes in boys, but not in girls (the highest maximum maternal hair level during pregnancy was 23.9 μg/g).*

*The New Zealand study found evidence of developmental retardation (according to the Denver Test) in 4-year-old children at average maternal hair mercury levels during pregnancy within the range of 6-86 μg/g (the second highest value was 20 μg/g). The New Zealand mercury values should be multiplied by 1.5 to convert to maximum maternal hair levels in pregnancy.*

# 10. EVALUATION OF HUMAN HEALTH RISKS

## 10.1 Exposure Levels and Routes

In view of the restrictions placed upon the use of methylmercury in most countries, occupational exposure will be low.

The major source of human exposure to methylmercury is through the diet, more specifically from the consumption of fish and fish products. In most countries, the important food fishes have methylmercury levels in their edible portion not exceeding 200-300 μg/kg. However, levels in such predatory species as ocean tuna, shark, and swordfish (even from non-polluted areas), as well as freshwater pike, walleye, and bass, may contain methylmercury levels in excess of 1000 μg/kg. In view of the worldwide variation in dietary patterns and extent of pollution, it is difficult to calculate a general exposure level for methylmercury. However, assuming an average daily consumption of 20 g of non-predatory species containing 200 μg/kg, the daily methylmercury intake would be 4 μg. It has been estimated that long-term intake at this level would raise the blood methylmercury levels by 4 μg/litre, and hair levels by 1 μg/g. However, in some countries the average consumption can be as high as 100 g/day and may consist mainly of predatory species. In these cases, methylmercury intakes can exceed 100 μg/day.

## 10.2 Toxic Effects

### *10.2.1 Adults*

Concerning the risks in adults exposed to methylmercury, the conclusions reached in Environmental Health Criteria 1: Mercury (WHO, 1976) and the 1980 interim evaluation remain unchanged. A daily methylmercury consumption of 0.48 μg/kg body weight (WHO, 1989b) will not result in any detectable adverse effects. However, a daily intake of 3-7 μg/kg body weight would cause adverse effects on the nervous system, manifested as an approximately 5% increase in the incidence of paraesthesia. Hair

concentrations would be approximately 50-125 μg/g at this level of intake. Clinical observations in Iraq suggested that women are more sensitive to the toxic effects of methylmercury during pregnancy.

### 10.2.2 Prenatal exposure

The report (WHO, 1980) that evaluated the health hazards from exposure to methylmercury through the consumption of fish underlined that damage to the fetal brain caused by prenatal exposure to methylmercury could be the critical effect, and that more information was needed for a proper risk assessment. Since 1980, experimental evidence to elucidate the mechanisms involved in the neurotoxic action of methylmercury on the fetal brain has accumulated and has been reviewed in this monograph. Further analysis of data from the Iraqi outbreak has extracted additional information relating to the effects of prenatal methylmercury exposure. From these sets of evidence, a pattern has emerged that permits the construction of a biological model for the neurotoxic action of methylmercury on the fetal brain.

Methylmercury inhibits the growth of the fetal brain and the migration of neurons from the embryological generation layer to the final destination in the brain cortex. This has been demonstrated in clinical cases in Japan and Iraq. An inhibition of brain growth is indicated by a decrease in brain size and weight, as was observed in studies on monkeys and humans. The inhibition of fetal brain development caused by methylmercury exposure results in the behavioural changes and reduced cognitive and motor ability found in clinical cases. It has been demonstrated that methylmercury interferes with microtubule formation, cell division, and neuronal protein synthesis, all of which could explain the effects described above.

The model emerging to explain the neurological effects of methylmercury is a continuous dose-effect relationship, with a range from subtle changes in brain function (indicated by psychological tests) at low dose levels to a severe neurological syndrome of cerebral palsy with pronounced changes in the organization of brain structure at high exposure levels. However, the possibility of

detecting and characterizing the methylmercury level at which the subtle and early adverse effects on the fetal brain may arise is limited by the availability of sensitive test procedures. At present, some effects can only be detected and adequately characterized in the epidemiological studies of fairly large populations.

The crucial question is the actual exposure level (or body burden) of methylmercury in humans which can lead to subtle changes in the offspring. The actual exposure levels and patterns are usually unknown, but the effect can be related to the hair mercury level and an approximate daily exposure calculated from the known kinetic parameters for methylmercury accumulation, distribution, and excretion.

The statistical analysis of data on 84 infant-mother pairs (maternal peak hair mercury levels during pregnancy of 0.4-640 μg/g) showed that, at maternal hair concentrations above 70 μg/g, children exhibited evidence of abnormal neurological signs, e.g., increased muscle tone in the leg and exaggerated deep tendon reflexes, often accompanied by ataxia together with a history of developmental delay. This statistical analysis indicated a 30% risk of these abnormal findings at maternal hair mercury concentrations around 70 μg/g. The data from the Iraqi outbreak do not permit firm conclusions to be drawn concerning the risk of adverse effects below that level. However, by applying the biological model described above, the extrapolation method of Cox et al. (1989), and the evaluation of other currently available data, it can be calculated that a maternal hair mercury concentration of 10-20 μg/g implies a 5% risk. The possibility cannot be excluded that effects detectable by psychological and behavioural testing or subclinical effects might occur at even lower levels of exposure, but evidence is lacking.

## 10.3 Conclusions

The general population does not face a significant health risk from methylmercury. Certain groups with a high fish consumption may attain a blood methylmercury level (about 200 μg/litre, corresponding to 50 μg/g of hair) associated with a low (5%) risk of neurological damage to adults.

The fetus is at particular risk. Recent evidence shows that at peak maternal hair mercury levels above 70 μg/g there is a high risk (more than 30%) of neurological disorder in the offspring. A prudent interpretation of the Iraqi data implies that a 5% risk may be associated with a peak mercury level of 10-20 μg/g in the maternal hair.

There is a need for epidemiological studies on children exposed *in utero* to levels of methylmercury that result in peak maternal hair mercury levels below 20 μg/g, in order to screen for those effects only detectable by available psychological and behavioural tests.

# 11. RECOMMENDATIONS

## 11.1 Gaps in Knowledge

In spite of significant advances in our understanding of the toxicity and potential hazard of methylmercury, there remain areas in which there is an urgent need for additional studies.

The most important of these areas is the lower end of the dose-response relationship for prenatal exposures. This will require well coordinated and designed, international epidemiological studies that consider all relevant confounding factors (e.g., drugs, alcohol, smoking). As part of these studies, there is a need to develop objective measurements of clinical manifestations. The potential ability of selenium and other dietary components (e.g., antioxidants) to alter the toxic responses elicited by methylmercury should be investigated. These studies will not only need to describe this interaction, but also to provide data that can be used quantitatively in a risk assessment of methylmercury, particularly for the fetus. The mechanisms of damage to both the mature and developing nervous system remain to be elucidated. As no information on the relative vulnerability of the brain during different periods of pregnancy is available, more experimental work is needed to shed light on this aspect, which is important for risk assessment and clinical judgement. The selective damage to the nervous system and to specific areas in the brain, the long period in the case of adult poisoning, and the high vulnerability of the developing nervous system (including sex differences in susceptibility) are still unexplained.

## 11.2 Preventive Measures

In populations that consume large amounts of fish (e.g., 100 g/day), the hair levels of methylmercury in women of child-bearing age should be monitored. If the results of these monitoring activities indicate excessive exposure to methylmercury, appropriate and practical measures, such as dietary recommendations, should be taken to reduce the possibility of long-term exposure during

pregnancy and to keep it below internationally recommended allowable intakes.

Measures to reduce methylmercury exposure via the consumption of fish will need to consider the impact of these measures on the overall dietary requirements of these individuals.

# 12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The human health risks from exposure to methylmercury were previously evaluated in Environmental Health Criteria 1: Mercury (WHO, 1976b). This was followed by a brief update (WHO, 1980), based upon a technical report prepared by the Monitoring and Assessment Research Centre (MARC, 1981).

In the thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), it was recommended that the permissible tolerable weekly intake (PTWI) for methylmercury in adults be maintained at 200 μg (3.3 μg/kg body weight) (WHO, 1978; WHO, 1989b). However, the Committee noted that pregnant women and nursing mothers are likely to be at greater risk, although the available data were insufficient to recommend a specific mercury intake for these population groups.

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

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# APPENDIX

Comparison between maximum hair levels of mercury during pregnancy and symptoms and signs in the mother and her offspring[a]

| | Mother | | | Child | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Symptoms | | | | | | Symptoms | | |
| Mother-infant number | Paraesthesia | Other | Mercury level (mg/kg) | Sex | Walked (month) | Talked (month) | Mental | Seizures | Neurological score |
| 2 | 0 | 0 | 1 | female | 12 | 24 | 0 | 0 | 2 |
| 3 | 0 | 0 | 1 | male | - | - | 0 | 0 | 2 |
| 5 | 0 | 0 | 1 | male | 14 | 12 | 0 | 0 | 0 |
| 6 | 0 | 0 | 1 | male | 18 | 18 | 0 | 0 | 0 |
| 7 | 0 | 0 | 1 | male | 18 | 24 | 0 | 0 | 3 |
| 9 | 0 | 0 | 1 | male | 13 | 26 | + | 0 | 3 |
| 13 | 0 | 1 | 1 | female | 12 | 12 | 0 | 0 | 4 |
| 14 | 0 | 0 | 1 | female | 18 | 26 | 0 | 0 | 2 |
| 18 | 0 | 0 | 1 | female | 16 | 16 | 0 | 0 | 0 |
| 19 | 0 | 0 | 1 | male | 12 | 12 | 0 | 0 | 0 |
| 26 | 0 | 0 | 1 | male | 12 | 14 | 0 | 0 | 0 |
| 31 | 0 | 0 | 1 | male | 11 | 12 | 0 | 0 | 1 |
| 33 | 0 | 0 | 1 | female | 12 | 20 | 0 | 0 | 2 |
| 39 | 0 | 0 | 1 | female | - | - | 0 | 0 | 4 |
| 41 | 0 | 0 | 1 | male | 11 | 18 | 0 | 0 | 3 |
| 69 | 0 | 0 | 1 | male | 18 | 20 | 0 | 0 | 4 |
| 4 | 0 | 0 | 2 | male | 18 | - | 0 | 0 | 0 |
| 8 | 0 | 0 | 2 | female | 13 | 18 | 0 | 0 | 0 |
| 10 | 0 | 0 | 2 | male | 16 | 18 | 0 | 0 | 3 |
| 11 | 0 | 0 | 2 | male | 12 | 24 | 0 | 0 | 3 |
| 12 | 0 | 0 | 2 | male | 18 | 18 | 0 | 0 | 3 |

Appendix (contd).

| Mother-infant number | Mother | | | Child | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Symptoms | | | | | | Symptoms | | |
| | Paraesthesia | Other | Mercury level (mg/kg) | Sex | Walked (month) | Talked (month) | Mental | Seizures | Neurological score |
| 16 | 0 | 0 | 2 | female | 18 | 18 | 0 | 0 | 2 |
| 27 | 0 | 0 | 2 | male | 12 | 10 | 0 | 0 | 0 |
| 32 | 0 | 0 | 2 | male | 14 | - | 0 | 0 | 0 |
| 47 | 0 | 0 | 2 | male | 18 | 24 | 0 | 0 | 3 |
| 1 | 0 | 0 | 3 | female | 14 | 18 | 0 | 0 | 0 |
| 21 | 0 | 0 | 3 | male | 18 | - | 0 | 0 | 1 |
| 23 | 0 | 0 | 5 | male | 12 | 12 | 0 | 0 | 1 |
| 34 | 0 | 0 | 6 | male | 12 | 10 | 0 | 0 | 0 |
| 38 | 0 | 0 | 6 | female | 18 | 10 | 0 | 0 | 2 |
| 35 | 0 | 0 | 7 | male | 12 | 18 | 0 | 0 | 0 |
| 29 | 0 | 0 | 8 | male | 18 | 19 | 0 | 0 | 0 |
| 40 | 0 | 0 | 9 | female | 12 | - | 0 | 0 | 0 |
| 20 | 0 | 0 | 10 | male | 12 | 12 | 0 | 0 | 2 |
| 24 | 0 | + | 10 | male | 14 | - | 0 | 0 | 3 |
| 22 | 0 | 0 | 12 | male | 18 | 14 | 0 | 0 | 1 |
| 28 | 0 | 0 | 12 | female | 14 | 18 | 0 | 0 | 2 |
| 17 | + | + | 14 | female | 20[b] | 18 | 0 | 0 | 1 |
| 36 | 0 | 0 | 16 | male | 18 | 16 | 0 | 0 | 5 |
| 42 | 0 | 0 | 18 | female | 36[b] | 30[b] | 0 | 0 | 0 |
| 25 | 0 | 0 | 19 | male | 12 | 18 | 0 | 0 | 2 |
| 30 | + | + | 23 | female | 12 | 12 | 0 | 0 | 1 |
| 37 | 0 | 0 | 26 | male | 12 | 12 | 0 | 0 | 1 |
| 15 | 0 | 0 | 38 | male | 20[b] | 18 | 0 | 0 | 6 |
| 49 | 0 | 0 | 45 | male | - | - | 0 | 0 | 4 |

Appendix (contd).

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 59 | 0 | 0 | 46 | male | 12 | 12 | 0 | 0 | 2 |
| 53 | 0 | 0 | 52 | female | 18 | 18 | 0 | 0 | 1 |
| 48 | + | + | 59 | female | 18 | 26[b] | 0 | 0 | 0 |
| 43 | 0 | 0 | 60 | male | 20[b] | 18 | 0 | 0 | 5 |
| 44 | 0 | 0 | 62 | male | 18 | 24 | 0 | 0 | 0 |
| 54 | + | + | 74 | male | 18 | 26[b] | 0 | 0 | 2 |
| 46 | + | 0 | 75 | female | 12 | 12 | 0 | 0 | 0 |
| 52 | + | 0 | 78 | female | 14 | 28[b] | + | + | 4 |
| 50 | 0 | 0 | 86 | male | 11 | 26[b] | 0 | 0 | 6 |
| 58 | 0 | + | 98 | female | 12 | 12 | 0 | 0 | 2 |
| 57 | 0 | 0 | 104 | female | 15 | 18 | 0 | 0 | 4 |
| 72 | 0 | 0 | 114 | male | 14 | 48[b] | + | 0 | 0 |
| 64 | 0 | 0 | 118 | female | 18 | 18 | 0 | 0 | 0 |
| 51 | + | + | 154 | male | 24[b] | 36[b] | 0 | + | 3 |
| 76 | 0 | 0 | 196 | male | 12 | 15 | 0 | 0 | 0 |
| 77 | 0 | 0 | 202 | male | 24[b] | 20 | 0 | 0 | 3 |
| 61 | 0 | + | 242 | female | 15 | 18 | + | 0 | 0 |
| 74 | 0 | 0 | 263 | female | 18 | 18 | 0 | 0 | 5 |
| 66 | 0 | 0 | 269 | male | 12 | 12 | 0 | 0 | 1 |
| 63 | + | 0 | 294 | male | 20[b] | 34[b] | + | + | 0 |
| 62 | + | + | 336 | male | 24[b] | 36[b] | 0 | + | 0 |
| 67 | + | 0 | 339 | female | 20[b] | 26[b] | 0 | 0 | 4 |
| 60 | + | 0 | 357 | female | 20[b] | 30[b] | 0 | 0 | 2 |
| 65 | + | 0 | 362 | male | 14 | 16 | 0 | 0 | 4 |
| 71 | + | + | 376 | female | 20[b] | 30[b] | 0 | + | 2 |
| 75 | 0 | 0 | 399 | male | 15 | 24 | 0 | 0 | 3 |
| 56 | + | + | 404 | male | 60[b] | 60[b] | + | + | 11 |
| 70 | + | 0 | 405 | female | 60[b] | 36[b] | + | 0 | 11 |
| 68 | 0 | 0 | 418 | male | 72[b] | 72[b] | + | + | 11 |
| 45 | 0 | 0 | 443 | male | 36[b] | 30[b] | + | 0 | 11 |
| 73 | 0 | 0 | 468 | female | 14 | 20 | 0 | 0 | 6 |

Appendix (contd).

| | Mother | | | Child | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Symptoms | | | | | | Symptoms | | |
| Mother-infant number | Paraesthesia | Other | Mercury level (mg/kg) | Sex | Walked (month) | Talked (month) | Mental | Seizures | Neurologica. score |
| 80 | 0 | + | 557 | female | 22[b] | 22[b] | 0 | 0 | 2 |
| 79 | 0 | 0 | 568 | female | 20[b] | 26[b] | 0 | 0 | 4 |
| 78 | 0 | 0 | 598 | male | 24[b] | 23 | 0 | 0 | 7 |
| 81 | + | + | 674 | male | 24[b] | 26[b] | 0 | 0 | 2 |

[a] From: Marsh et al. (1987)
o = absence of abnormality.
+ = presence of abnormality.
- = no observations were made.
[b] Abnormal value.
For further details, see section 9.4.2.1.

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