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Recommendations for Epidemiological Research on Mercury

Report from a WHO consultation at the
National Institute for Minamata Disease, Minamata City, Japan
10–13 October 1993

Epidemiological studies of mercury compounds, particularly methylmercury, have been of great importance in the assessment and control of mercury-associated environmental disease outbreaks. High exposure to mercury compounds continues to occur, however, particularly among indigenous groups who consume large quantities of fish, and in developing countries in which alluvial gold mining is carried out. A WHO informal consultation on mercury epidemiological research, held at the National Institute for Minamata Disease in Japan in 1993, drew up various proposals for future research. As a follow-up to this consultation, WHO has prepared an international guideline on how epidemiological studies of mercury should be carried out.

December, 1994

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The meeting was opened by Dr Tord Kjellström on behalf of Dr Hiroshi Nakajima, Director-General of WHO, and Dr ST Han, Regional Director of the WHO Western Pacific Regional Office. Dr Kjellström stressed the importance of producing feasible guidelines for conducting surveys in developing countries where mercury pollution may constitute a health hazard. The purpose of this consultation was to exchange information on current epidemiological research in this area and to advise on the development of guidelines for future studies.

Dr Brian Wheatley was elected as Chairman of the meeting, Dr Hiroo Kato as Vice-Chairman, and Dr Philippe Grandjean as Rapporteur.

The participants (see Annex 1) presented ongoing studies of mercury exposure and mercury toxicity at an International Symposium in Kumamoto. These have been published by the National Institute for Minamata Disease in a separate publication (see Annex 2). Mercury analysis techniques used at the National Institute for Minamata Disease were demonstrated. A working paper on *Practical guidelines for environmental epidemiology studies: methylmercury and other mercury compounds* (prepared by Dr Grandjean) was reviewed; the main part of the discussion focused on the methodologies for mercury epidemiology research and the recommendations for WHO activities with regard to coordination and collaboration in this area.

Purpose and outline of environmental epidemiology studies

Releases of mercury into the environment are increasing and have become a potential health hazard in many parts of the world. Exposure to mercury is most commonly associated with consumption of fish contaminated with methylmercury, and with release of mercury vapour during "informal" gold-mining operations and industrial processes in certain developing countries. In addition, some mercury vapour exposure emanates from dental amalgam, but the health significance of this is widely debated. Care should be taken to distinguish between these different types of exposure. In the case of **methylmercury contamination** of fish, the resultant potential health risk may be widely disseminated and insidious, for instance among indigenous populations in the Amazon. But in the case of mercury vapour, as found in some gold-mining areas in the Amazon basin, the resultant health hazard is due rather to **occupational exposure** and therefore limited to the immediate vicinity of the gold refining operation (amalgamation and amalgam burning). Nevertheless, large numbers of gold miners and their families are exposed.

In particular, exposure surveys and epidemiological studies are needed to guide preventive efforts and to improve scientific understanding of the human health effects of mercury. **Descriptive exposure surveys** should be carried out as a first step. The studies could begin with simple cross-sectional surveys to be supplemented later by more complex studies of the sources of exposure. If high exposures are found, these can be investigated further by undertaking detailed **epidemiological studies**. But the more advanced epidemiological designs may require substantial investments of resources and time, and results may emerge only after a considerable delay. Thus in most situations, exposure surveys will provide the best immediate guidance for preventive action.

Epidemiological studies must take into account the availability of **appropriate technology** and the feasibility of methodologies. For example, if power sources are unreliable it will not be possible to keep biological samples frozen. Similarly, delays in transportation of samples to the laboratory will render some analytical techniques inappropriate. The methodology for defining the target population will also vary, according to the situation in each country. If relevant health statistics, e.g. on pregnancies and births, are not available, it may prove impossible to identify representative subsamples of the population. Lack of vital statistics and population records would also make it difficult to contact patients for a repeat examination in follow-up studies.

The time frame of epidemiological studies is important. While cross-sectional surveys are useful, **repeated and comparable studies** are sometimes even more so, since they may reveal temporal changes, e.g. increasing severity of a pollution problem, effectiveness (or otherwise) of preventive efforts. The potential for repeating a survey with the same design at a later stage must therefore be considered when designing the study, as should biological data banks, and long-term storage of samples (to enable re-analysis later, when earlier samples are compared with new ones).

Quality assurance is important at every step. Samples must be collected from representative groups of individuals, and they must be stored and transported under acceptable and well-defined conditions. The analytical methods must have a high precision and be of acceptable accuracy, and both must be documented on a routine basis by internal and external quality assurance procedures. Reference materials, including human hair, are needed for this purpose and should contain mercury at relevant concentrations. International quality assurance systems established by WHO, IAEA and certain national laboratories can serve as guides for local laboratories.

The general recommendations made above will be expanded upon in the following sections. Additional ideas can be gleaned from recommendations for future research included in the WHO *Environmental health criteria* on different mercury compounds (see Annex 3). Epidemiological studies of the health hazards arising from mercury exposure require cooperation between multiple research disciplines, authorities and local groups. This is because the health effects resulting from mercury exposure are varied and difficult to measure clinically, and because exposure assessment requires field sample collection in the community.

Exposure surveys concerning contaminated fish and other specimens

If methylmercury exposure is due to consumption of contaminated fish or any other food source such as sea mammals, then the **mercury concentration in hair** would be the most reliable indicator. An initial exposure study that includes measurement of the mercury content of hair can be very informative, provided occupational exposure to mercury vapour has been ruled out. If individuals with a high mercury content in hair are found, and exposure from fish is suspected, **dietary surveys** would be useful for clarifying eating patterns (i.e. the amount of fish eaten, the identity of the fish species, the origin of the fish) as well as the distribution of size and age. In some areas of the world, ingestion of marine mammals, birds and birds' eggs must be considered as well. If this is the case, a form of food frequency questionnaire can be used, but seasonal differences must be taken into account.

Analysis of fish should focus on large, frequently-consumed species that are known to be predators at the top of the food chain. Only edible parts should be analyzed, i.e. sometimes the whole fish, sometimes not. If indicated, seasonal sampling should be carried out. Some of the mercury may be inorganic mercury (i.e. mercuric ion); the proportion will vary between species. Accordingly, **speciation of the mercury content** should be performed for each fish species that has been consumed in significant quantities, to provide guidance for interpreting data relating to total mercury concentrations. The same applies to those parts of marine mammals that are consumed by certain populations in the Arctic and subarctic areas. High levels of inorganic mercury are found primarily in the liver of such mammals. It should be noted that cooking and other preparatory techniques do not change the speciation or amount of mercury in food. Analysis of the mercury levels of cats and other animals that consume fish may also be worthwhile in polluted areas.

Long-term methylmercury exposure from fish is closely correlated with the mercury concentration in hair of the individual concerned. However, scalp hair may have already become contaminated, e.g. by mercury vapour. So if the mercury concentration of a hair sample exceeds a certain level, such as 10 mg/kg, and occupational exposure or other external contamination is suspected, speciation of the mercury found in the hair would be worthwhile. If long hair strands can be obtained, the temporal exposure pattern can be ascertained by analysing short segments of hair separately. A 10 mm segment represents about one month of hair growth. Segmented analysis gives information about peak exposure level (for the time period covered by the length of the segment). Seasonal hair sampling can also provide information relating to temporal exposure — this can be especially useful if only short hair strands are available. Some epidemiological studies have used the peak mercury concentration in hair as the marker for exposure, while other studies have used the average mercury concentration. The ratio between the two parameters is likely to vary depending on the time variability of the exposure. In many tropical areas there is a great diversity of fish, which often means that dietary habits vary from season to season. Mercury levels along strands of hair may vary considerably as a result. The toxicological significance of the peak or the average hair mercury concentration is not yet known and further research on this issue is required. If possible, therefore, both the **average and the peak mercury concentration** should be measured and evaluated.

Groups at risk of high methylmercury exposure include fishermen and their families, as well as other groups with known or estimated high intake of fish. Fetuses of pregnant women and infants are especially susceptible to health impacts arising from exposure to mercury. Exposure surveys should therefore pay particular attention to these groups.

Evidence is accumulating that the Amazon basin is becoming contaminated with mercury. In addition, hydroelectric dams in Canada and elsewhere are now known to cause conditions that contribute to methylmercury accumulation in fish in reservoirs. Freshwater fish and marine fish generally vary in their content of **selenium or essential fatty acids**. Some experimental studies indicate that selenium may protect against the effects of mercury toxicity. Data on such parameters may therefore be useful for interpreting related epidemiological studies.

Exposure surveys for occupational exposure

If occupational exposure to mercury vapour has occurred, the **concentration of mercury vapour in air** can be measured by relatively simple methods. Measurements should preferably emphasize average levels during the day, but short-term measurements (less than 15 minutes) are useful for characterizing the significance of individual sources of exposure. The indirect exposures that may reach bystanders, i.e. individuals who are not directly involved in the occupational process but who may be exposed due to their proximity to the workplace, should also be estimated.

In the case of mercury vapour (and inorganic mercury compounds), the mercury **concentration in urine** is the best marker of human mercury accumulation. Ideally, the first morning urine should be collected on three different mornings. The sample should represent the urine production of the entire preceding night. Urine samples of either a very low or very high density, or creatinine concentrations, can confuse the exposure assessment. Adjustment can be made by recalculating the urine concentrations to a fixed density or by dividing the mercury concentration with the creatinine concentration.

For further study of exposure to either methylmercury or mercury vapour, autopsy tissue specimens can be analyzed for mercury content. It should also be pointed out that in many cases specimens can be collected and stored for later analysis. Hair specimens are easy to store. Other specimens are best stored frozen. Freezing does not affect the speciation or concentration of mercury compounds.

Measurements of health effects

Health effects of environmental mercury intoxication may be due to exposure to inorganic mercury (through ingestion or inhalation), methylmercury (usually from ingestion), or some combination of inorganic and organic mercury. The effects of such exposures differ depending upon the mercury speciation, the dose, and when the exposure occurred, i.e. prenatally or postnatally.

After an exposure assessment has determined that high exposure is indeed occurring, an epidemiological study should be undertaken. It should consist of a more extensive, detailed and comprehensive assay of exposure and measurement of biochemical, physiological or clinical effects. Study protocols should apply a minimum set of evaluation techniques to assay effects, and those techniques should be widely understood, straightforward methods that are available and perhaps even already in use at the sites being studied. Separate protocols should be used for children and adults.

None of the effects of methylmercury toxicity can be considered specific for methylmercury poisoning. But the total clinical picture, i.e. the combination of signs and symptoms and confirmed high individual exposure, may indicate methylmercury poisoning as a cause. **In congenital cases, the early effects are generally non-specific.** In severe cases in Japan, the effects were diagnosed as severe cerebral palsy. In reports from other exposed areas, delayed developmental milestones, clumsy movement and various degrees of mental retardation were observed for "severe" cases. **In adults, sensory disturbances** (paraesthesias of the glove-stocking type), **constriction of the visual field** and **ataxia** are major signs; other typical effects include hearing deficit (especially at high frequencies), and impairment of gait and speech, and abnormal eye movement.

For adults exposed to high levels of methylmercury (e.g. blood levels exceeding 200 $\mu g/l$), peripheral nervous system function should be determined by assessing numbness (by questionnaire and by determining the vibration sensitivity threshold) and muscle strength (by determining grip force). Central nervous systems function, sensory function and mental function should also be tested, particularly if a complete health effects assessment is intended and feasible. An epidemiological study could be based on a careful selection of some of the following tests:

- examination of central nervous system function; this includes evaluation of possible ataxia and motor co-ordination (gait assessment, diadochokinetic rate, finger tapping, hand-eye coordination test, finger-to-nose test, foot-to-knee test, Romberg Test), and visual field and eye movement testing

- examination of sensory function; this includes assessment of vision (perimetry), hearing (audiometry, accompanied by tympanometry and otoscopy), and tactual performance (e.g. form board)

- examination of mental function; this includes determining mental status and cognitive functions.

For children who were exposed to high doses of methylmercury in the womb, peripheral nervous system function can be assessed by grip force. Central nervous system function can be determined by assessing motor coordination and the degree of ataxia, using tests similar to those used for adults. Sensory tests in children could include the Beery-Buktenica Developmental Test of Visual Motor Integration, and tests for auditory-perceptual and tactual function similar to those used for adults. Cognitive function tests would include tests of intelligence and general ability; tests must be culturally and linguistically relevant. If may not be feasible to carry out complete testing, but a careful selection of tests would still enable an epidemiological analysis to be made. The specific effects on children of exposure to low doses of methylmercury — as a result of maternal consumption of fish for example — have yet to be determined. Therefore, a set of "preferred tests" cannot be listed.

The effects of mercury vapour also vary according to the age of the individual. In adults, chronic occupational **exposure to mercury vapour can lead to tremor and other neurobehavioural effects**, such as memory disturbance and erethism, i.e. emotional lability, shyness and insomnia. Sensorimotor neuropathy may also be seen. Chronic exposure to mercury vapour can lead to an accumulation of inorganic mercury in the kidneys and kidney dysfunction. In children, a syndrome called acrodynia ("pink disease") may be seen. It consists of pain, swelling and pink coloration of fingers and toes, irritability, failure to thrive, photophobia, profuse perspiration, and is sometimes accompanied by rashes.

In adults exposed to mercury vapour, peripheral nervous system function should be determined by assessing vibration sensitivity threshold and muscle strength (grip force). Examination of central nervous system function should include evaluation of motor co-ordination (diadochokinetic rate, finger tapping, hand-eye coordination test, finger-to-nose test, foot-to-knee test). Tactual performance can be evaluated by a form board test. Mental function should be examined by determining mental status and cognitive functions. Kidney function should be assessed by dip-stick test for proteinuria, and positive results should be followed by more specific determination of levels of albumin and other proteins.

In children exposed to mercury vapour, the clinical examination should pay particular attention to the signs of acrodynia mentioned above. Information currently available does not permit any specific recommendations to be made concerning the most appropriate tests for determining the early effects of mercury vapour toxicity in children. However, tests similar to those used for methylmercury-exposed children can be useful.

Approaches to epidemiological study designs

The design of surveys and in-depth studies of mercury exposure and mercury toxicity should incorporate the step-wise approach to investigating the extent and severity of the problem by:

- determining whether a problem is present
- quantifying and further characterizing the problem
- linking possible adverse health effects to the causal exposure
- evaluating the effect of interventions.

As a first step, the suspected problem must be defined, e.g. whether both inorganic and methylmercury exposures may be involved. Then the background literature should be consulted for suggestions concerning which endpoints to investigate, evidence of dose–effect and dose–response relationships, etc. Potential exposure and effect variables must then be chosen, so that the study design can be prepared. Several WHO documents contain useful information on the general epidemiological approaches and should be consulted. (A list of key references is included in Annex 2.)

A proposed study of mercury exposure will often benefit from being combined with other public health studies, such as screening for important diseases. Ideally, individually-based exposure and effect data should be collected, and so-called "ecological" studies avoided (see Beaglehole, Bonita and Kjellström, 1993). Most studies are likely to be exposure-driven, i.e. aim at determining the degree of exposure and its possible effects. Studies may also be disease-driven, i.e. aim at determining the cause (causal exposure) of the disease or adverse condition; in this situation, a case–control design will be useful.

In studies of the early effects of methylmercury, the significance of other, potentially confounding factors must be taken into account. Thus social factors, e.g. factors relating to the home environment, have a significant influence on the nervous system development of children and could confound a relationship between mercury exposure and neurobehavioural dysfunction. Other factors that could be potentially confounding in studies of adults include alcohol and drug consumption, as well as occupational exposure to other neurotoxins. Anthropological and social issues must also be considered when evaluating the information obtained from exposed populations, e.g. life-style changes due to the perceived danger of consuming fish.

Other than in the most severe cases, a patient's mercury exposure cannot be considered as a specific cause of a mercury-associated effect. The association is statistical and valid only on a group basis. This fact must be communicated to the exposed population(s) along with the outcome of the examinations.

Risk management

Decisions on preventive efforts should be based on current knowledge, as reviewed, for example, in the WHO *Environmental health criteria no. 101: methylmercury*, (1990, pp. 104–5). If high exposures have been documented, appropriate actions to reduce exposures should not be delayed as a consequence of decisions to carry out epidemiological studies.

A balanced approach must be adopted when making decisions concerning risk management. Thus the safety and availability of alternatives to contaminated food or polluting processes, and the wider ranging social and health-related effects of an intervention should be considered together with means of reducing mercury release and mercury absorption.

Risk management should generally include both primary prevention and health education. Primary prevention would aim to remove the source of exposure, whenever possible. In addition, targeted health education for individuals or groups at particular risk can be used to highlight individual actions that reduce exposure, and the health risks of continued exposure. The information provided should distinguish between toxic risks within an exposed group and specific signs of mercury toxicity in an individual.

The human fetus is especially vulnerable to methylmercury toxicity — it can suffer serious neurotoxic effects at exposures that do not cause discernible toxicity in the mother. Women of child-bearing age should therefore be targeted for specific prevention efforts, including health education.

Annex 1: List of participants

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Annex 2: Key references

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Annex 3: IPCS recommendations

The International Programme on Chemical Safety (IPCS) is a collaborative programme between WHO, UNEP (United Nations Environmental programme) and ILO (International Labour Organisation). This collaboration is currently being extended to several additional international agencies who have specific responsibilities for the safety aspects of chemicals.

In recent years, IPCS has published three comprehensive international reviews on mercury hazards in its *Environmental health criteria* (EHC) series. These are: *Environmental health criteria no. 86: mercury, environmental aspects* (1987); *Environmental health criteria no. 101: methylmercury* (1990) and *Environmental health criteria no. 118: inorganic mercury* (1991). Each *Environmental health criteria* publication is prepared by a task group of international experts in consultation with scientific agencies in all countries.

We have summarized below the research recommendations contained in *EHC no. 101* and *no. 118* in order to promote their incorporation in future epidemiological studies.

Recommendations for further research from *EHC no. 101: methylmercury*

- **Gaps in knowledge**

Areas remain in which there is an urgent need for additional studies. The most important of these concerns the lower end of the dose–response relationship for prenatal exposures. Well-coordinated and well-designed international epidemiological studies are required that consider all relevant confounding factors (e.g. drugs, alcohol, smoking). These studies will need to develop objective measurements of clinical manifestations.

The potential ability of selenium and other dietary components (e.g. antioxidants) to alter the toxic effects caused by methylmercury should be investigated. Studies will need to describe this interaction and provide data that can be used quantitatively in risk assessment of methylmercury, particularly in relation to 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 fetal 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.

- **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 ensure that intake does not exceed internationally recommended allowable levels.

Measures to reduce methylmercury exposure that results from consumption of fish will need to consider the impact of such measures on the overall dietary requirements of the individuals concerned.

Recommendations for further research from *EHC no. 118: inorganic mercury*

Further research is required in the following areas:

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

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

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

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

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

6. The neurobehavioural effects of mercury in occupationally exposed populations (dentists, etc.).

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

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

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