

Biological monitoring of exposure to mercury vapor

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BARREGÅRD L. Biological monitoring of exposure to mercury vapor. *Scand J Work Environ Health* 1993;19:45–9. Biological monitoring of mercury in whole blood (B-Hg) or urine (U-Hg) can be used to assess exposure to mercury vapor if the kinetics and other sources of variation are taken into account. Its rapid rise postexposure makes B-Hg a good indicator of recent exposure peaks, while U-Hg (corrected for urinary flow rate) reflects average long-term exposure. However, high intraindividual variation sometimes requires the average of several U-Hg determinations. In the general population, methylmercury from fish and mercury from dental amalgam influence B-Hg and U-Hg, respectively, and must be considered if other exposures are being monitored. The quantitative relations between mercury in biological fluids and critical organs are poorly understood. Monitoring U-Hg is useful for assessing the risk of adverse effects and the need for preventive measures. At average U-Hg levels of about $50 \mu\text{g} \cdot \text{g creatinine}^{-1}$ ($28 \text{ nmol} \cdot \text{mmol creatinine}^{-1}$) the prevalence of symptoms and slight objective changes in the central nervous system and the excretion of certain urinary proteins are increased.

Key terms: adverse effects, amalgam, blood, central nervous system, critical organ, exposure, kidney, mercury vapor, occupational, review, urine.

Exposure to metallic mercury vapors may be high in certain work environments, for example, in mercury mines, the chloralkali industry, and plants for the production of fluorescent tubes, thermometers and alkaline batteries (1–7). The largest number of persons occupationally exposed to mercury vapors is found in dentistry, but current exposure levels are generally much lower than in industry (4, 8–9). In the general population, diet is the source of exposure to methylmercury, while inorganic mercury compounds in food are less important (2, 10). In countries where mercury amalgam is used for dental fillings, release from dental amalgam is the major source of inorganic mercury (1–2).

Biological monitoring is used to assess (i) exposure (environmental monitoring), (ii) absorbed dose, body burden or concentration in critical organ(s), or (iii) risk of adverse effects (health monitoring) (11). This review summarizes the usefulness of biologically monitoring exposure to mercury vapor with special reference to recent studies on kinetics, exposure from amalgam, and low or moderate occupational exposure.

Media, sampling and analysis

The main media used for monitoring are urine and whole blood, while there are fewer data for plasma,

serum, and erythrocytes (1–2). Mercury in feces, saliva, exhaled air, cerebrospinal fluid, or body organs, determined by means of in vivo X-ray fluorescence, has only been used sporadically.

Avoiding contamination in sampling is crucial. Urine should be collected in glass or plastic containers that have been acid-washed or found to be free of mercury. In the case of occupational exposure a urine sample should be collected at home after the subject's hands have been washed. Theoretically, 24-h urine is preferable, but in practice it is difficult to obtain without supervision, since there is a risk that not all the urine will be obtained. Furthermore, in occupational exposure, obtaining uncontaminated samples during workhours may be difficult. As a surrogate for timed samples, spot samples of the first morning urine, corrected for creatinine or specific gravity, are recommended. Venous blood is collected in mercury-free heparinized vacutainers in an uncontaminated environment.

If blood and urine samples are stored in a refrigerator for a few days or in a freezer for a couple of months, there is little risk of mercury loss from the samples by evaporation or irreversible adherence to the walls of containers. It is recommended, however, that urine samples be carefully homogenized before their analysis. It may be necessary to add a small amount of acid to elute any mercury from containers or precipitated salts (2).

The standard analytical method for mercury in whole blood (B-Hg) and urine (U-Hg) is cold vapor atomic absorption spectrophotometry after digestion of the samples with acids and reduction of bivalent mercury to mercury vapor, for example, with stannous chloride (1–2). The current detection limit is generally about $0.5 \text{ ng} \cdot \text{g}^{-1}$ for a 1-g sample, and the

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precision is about 5%. This is sufficient for most purposes, but, if a lower detection limit is needed, radiochemical neutron activation analysis, atomic fluorescence spectrometry, or other types of atomic emission spectrometry can be used. Quality assurance should include the analysis of external reference samples (in similar media and concentration ranges) in the same series as the unknown samples (1).

The average values of B-Hg and U-Hg in groups of occupationally unexposed individuals with low or moderate fish consumption are approximately $3 \mu\text{g} \cdot \text{l}^{-1}$ ($15 \text{ nmol} \cdot \text{l}^{-1}$) (12) and $4 \mu\text{g} \cdot \text{l}^{-1}$ ($20 \text{ nmol} \cdot \text{l}^{-1}$) respectively (1). For U-Hg corrected for creatinine, the average level in Swedish subjects is $2\text{--}3 \mu\text{g} \cdot \text{g}^{-1}$ ($1\text{--}2 \text{ nmol} \cdot \text{mmol}^{-1}$) (9, 13–14).

Influence of kinetics

After mercury vapor is inhaled, mercury is effectively and quickly absorbed, and the B-Hg level increases rapidly. If the exposure ceases, the maximum value of B-Hg is seen on the day of exposure, after which it decreases, with a half-time of about 3 d after a single low-level exposure (15). If exposure continues at the same level, the B-Hg will increase further and finally reach a steady state. After 3 d of high ($>100 \mu\text{g} \cdot \text{m}^{-3}$) exposure to mercury vapor, elimination from blood can be described by a two-compartment model with half-times of 3 and 18 d (16), the fraction of the fast phase accounting for about 80% of the initial maximum B-Hg (figure 1). After

long-term exposure, the fast phase has a similar half-time, but it accounts for only about half the B-Hg measured when exposure ceases (17). Its rapid rise after exposure makes B-Hg an excellent indicator of recent peaks in mercury exposure.

From the blood, mercury vapor is distributed to various tissues, where it is oxidized to bivalent mercury and bound to proteins. Oxidation also takes place in erythrocytes. After some time most of the mercury can be found in the kidneys. Elimination occurs mainly via urine and feces, and to a small extent via exhalation and sweat (2). Since mercury is not eliminated from the blood simply by glomerular filtration, but via some kind of tubular excretion, the rise in U-Hg is delayed as compared with the increase in B-Hg. After short-term exposure, the maximum U-Hg is not seen until several weeks after exposure. The half-time is then 40–60 d, if a one-compartment model is assumed (16). In a study of workers exposed for long periods the half-time was found to be about three months (18). In cases of unstable long-term exposure, the fluctuations in the concentrations of mercury in air should be expected to be “smoothed out” when U-Hg is measured. This phenomenon makes U-Hg a valuable indicator of average long-term exposure, but less useful for detecting temporary peaks or gaps in exposure.

There are few human data on the metabolism of inorganic mercury compounds after inhalation. Their lipid solubility is much less than that of mercury vapor, distribution to the tissues after exposure is slower, and the maximum levels in the brain are lower (1, 2). After oral experimental exposure to inorganic mercury compounds, the half-time in blood was three to four weeks (1). The average whole-body half-time was 42 d, and since the kidney is the major mercury depot, both after exposure to mercury vapor and after exposure to bivalent mercury, the U-Hg kinetics can be expected to be similar for the two species.

B-Hg % of initial (minus base line)

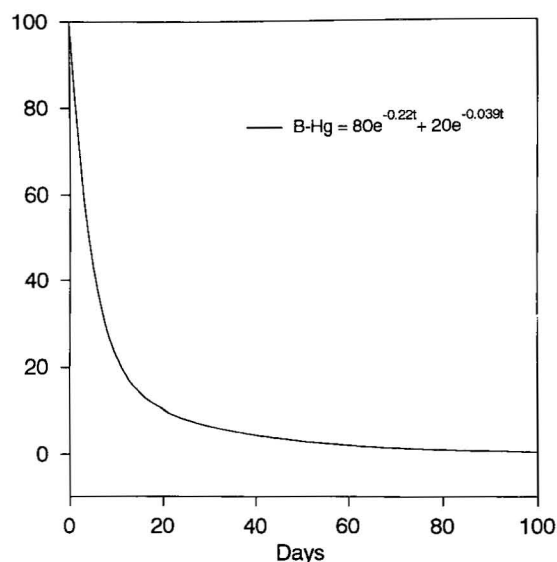


Figure 1. Two-compartment model (line) fitted to the exponential decrease in mercury in whole blood (B-Hg) in eight subjects after 3 d of high ($>100 \mu\text{g} \cdot \text{m}^{-3}$) exposure to mercury vapor (16).

Intra- and interindividual variation

“Natural” intraindividual variation in B-Hg is moderate, the coefficient of variation being about 10% if exposure is stable (19), whereas changes caused by exposure, whether attributable to occupation, food or dental amalgam, are rapid. The day-to-day variation in U-Hg, however, is relatively high even when 24-h samples are used under stable exposure conditions. When a correction for specific gravity or creatinine is made, typical coefficients of variation are 15–20% (16, 17, 20). Therefore U-Hg concentrations fluctuate around an average value, and the levels on two consecutive days often differ by 25%, but sometimes by 50%. If U-Hg is not corrected for hydration, the variation is even larger. For statistical reasons, if the exposure of a group of subjects is evaluated, the average is only slightly affected by this variation. When an individual’s exposure is moni-

tored, for example, in order to keep the level below a certain limit, this intraindividual variation is a serious disadvantage. An example, illustrated in figure 2, is the case of a biological limit of U-Hg for temporary removal from occupational exposure. Another problem arises when dose-response relations are evaluated on the basis of U-Hg as the dose indicator. The simplest solution to the problem is to use the average of several measurements either as the basis for decisions or as the exposure variable.

Total mercury in whole blood (B-Hg) is the sum of organic mercury (mainly methylmercury) and inorganic mercury (figure 3). Therefore, methylmercury intake from the consumption of fish is a disturbing factor when B-Hg is used for monitoring exposure to mercury vapor. The influence of fish consumption on B-Hg is shown in figure 4. In many countries half or more than half of the total B-Hg is methylmercury, which means that B-Hg is unsuitable for monitoring low-level exposure to mercury

vapor. The problem can be overcome if the inorganic mercury and methylmercury are analyzed separately. Some guidance can also be obtained from a comparison of the total mercury concentrations in plasma and erythrocytes, the latter containing about 90% of the methylmercury in whole blood.

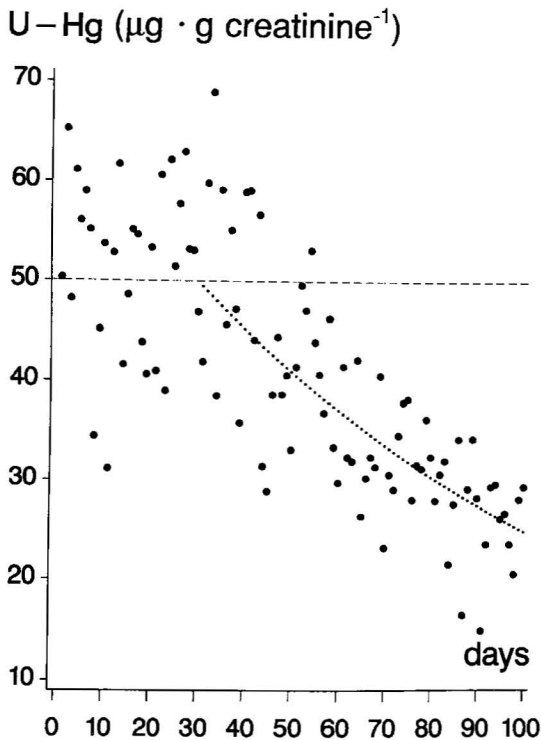


Figure 2. A simulated data set (normally distributed random numbers) showing the daily variation in creatinine-corrected urinary mercury (U-Hg) excretion. The average U-Hg during the first 30 d (stable exposure postulated) is $50 \mu\text{g} \cdot \text{g creatinine}^{-1}$ with a coefficient of variation of 18% (16, 20). Exposure then ceases and U-Hg decreases exponentially (16, 18) with an elimination constant of 0.01 (half-time 69 d). The dots indicate single U-Hg values, the curved line of dots the decrease in the average U-Hg, and the broken line a hypothetical biological limit value of $50 \mu\text{g} \cdot \text{g}^{-1}$ for removal from exposure. Note the large variation in U-Hg on some consecutive days, and the fact that single U-Hg values may still exceed the $50 \mu\text{g} \cdot \text{g}^{-1}$ limit one month after removal from exposure.

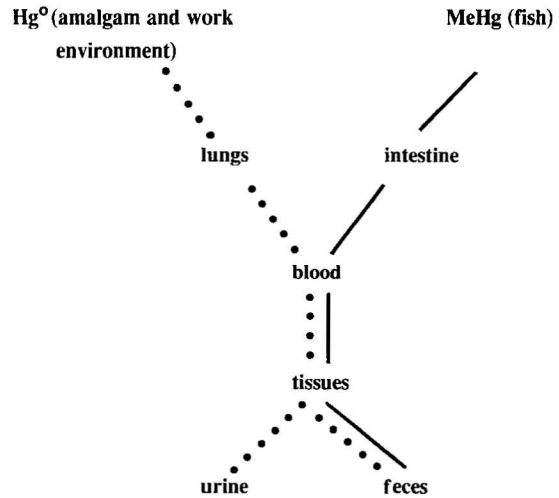


Figure 3. Diagram showing that mercury (Hg) in whole blood reflects exposure to both inorganic mercury and methylmercury (MeHg), while urinary mercury mainly reflects exposure to inorganic mercury. (Hg^0 = mercury vapor)

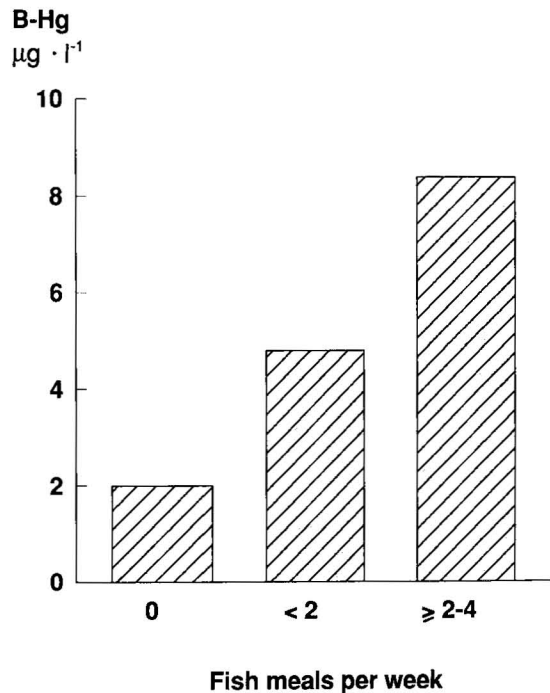


Figure 4. Influence of fish consumption on mercury in whole blood (B-Hg) in the general population. Based on data from Brune et al (12). ($1 \mu\text{g} \cdot \text{l}^{-1} = 5 \text{ nmol} \cdot \text{l}^{-1}$)

In cases in which there is no occupational mercury exposure and no large methylmercury intake, uptake from dental amalgam, if present, accounts for most of the exposure to inorganic mercury (1—2). If the objective of biological monitoring is to assess low-level exposure other than from a subject's own amalgam, the dental status must be recorded and adjusted for. This necessity is illustrated by a study of U-Hg levels in dental personnel, showing that their own dental fillings and their occupational exposure contributed to their U-Hg levels to about the same extent (9).

Assessing the exposure

Under constant long-term exposure conditions, the group average ratios between mercury in air ($\mu\text{g} \cdot \text{m}^{-3}$), U-Hg ($\mu\text{g} \cdot \text{g creatinine}^{-1}$), and B-Hg ($\mu\text{g} \cdot \text{l}^{-1}$) were reported to be 1:1.22:0.45 (7). Other ratios have been reported, but the study cited is probably the most reliable. The air mercury concentrations were measured with personal samplers, and the exposure was shown to be relatively constant during the 5-d study. The biological mercury analyses were quality controlled. Data on low-level exposure in dental personnel (1, 4, 8—9) indicate ratios between mercury in air and urine of the same magnitude. In conclusion, biological monitoring of B-Hg or U-Hg is suitable for assessing exposure to mercury vapor, provided that the kinetics and sources of variation are taken into account.

Assessing the dose and organ concentration

Biological monitoring is the most useful when levels in biological fluids can be used to predict the absorbed dose, body burden, and concentrations in critical organs. Unfortunately, this is not yet the case for mercury vapor or other forms of inorganic mercury (1). U-Hg is probably proportional to the mercury level in the kidney (2, 21) and thus to body burden. However, the quantitative data on such relationships are extremely limited. There is some information from Swedish nonoccupationally exposed subjects indicating that long-term absorption of 5—10 $\mu\text{g} \cdot \text{d}^{-1}$ will result in brain cortex mercury and kidney mercury of about 10 $\mu\text{g} \cdot \text{kg}^{-1}$ and 500 $\mu\text{g} \cdot \text{kg}^{-1}$, respectively (1). The estimated absorption is, however, very uncertain. As has already been stated, the corresponding levels of B-Hg and U-Hg could be expected to be about 3 $\mu\text{g} \cdot \text{l}^{-1}$ (part of which is methylmercury) and 2—3 $\mu\text{g} \cdot \text{g creatinine}^{-1}$, respectively. According to data on the half-times of mercury in blood, urine, brain, kidneys, and "whole body," some theoretical estimates which do not deviate too much from the aforementioned figures have been made concerning these relationships (22). For obvious reasons there are no hard data from empirical studies

linking these levels in the same individuals. Even less is known about possible relationships between the levels in biological fluids and organs at higher exposures.

Assessing the risk of adverse effects

Acute exposure to very high concentrations of mercury vapor causes pneumonitis. The classic effects of chronic poisoning, presented as mental changes (erethism), tremor and gingivitis, have been reported since the 16th century. Nephritis and allergic dermatitis are among the other well-known diseases that can be caused by exposure to inorganic mercury (1—2). Severe cases of mercury poisoning with erethism, classical mercurial tremor, or nephrotic syndrome are now rare, and even absent in many countries. In occupational settings a high (>10%) frequency of mercury poisoning has been reported when group averages for U-Hg were above 300 $\mu\text{g} \cdot \text{l}^{-1}$ (1500 nmol $\cdot \text{l}^{-1}$) (23—24).

Biological monitoring has proved useful when more nonspecific or subtle effects on the central nervous system and the kidneys are screened for, and these effects are related to the extent of exposure. An increased prevalence of symptoms and slight objective changes in the central nervous system seem to occur with long-term exposure to mercury vapor at levels above 50 $\mu\text{g} \cdot \text{m}^{-3}$, resulting in U-Hg concentrations of 50—100 $\mu\text{g} \cdot \text{g creatinine}^{-1}$ (1—2). These effects include symptoms such as fatigue and memory disturbances (25) or slight objective changes in short-term memory or tremor (26—29). Some studies suggest that such effects may occur at even lower levels (5—6, 30—31).

Elevated excretion of high-molecular weight proteins indicating a glomerular effect, or of tubular enzymes, has been observed at similar or slightly lower exposure levels, and enzymuria may possibly be the first objective effect (2, 13, 32).

The knowledge of possible relationships with adverse effects is much more limited for B-Hg than for U-Hg. In long-term exposure with fluctuating levels, U-Hg should be suitable for use in health monitoring. Biological monitoring is of little value in the case of local effects of mercury, such as pneumonitis or dermatitis. This is also the case when mercury salts are ingested, for example, in attempted suicide. In children, the occurrence of acrodynia has been reported in a small fraction of cases after exposure to inorganic mercury salts with U-Hg levels reported to be 50 $\mu\text{g} \cdot \text{l}^{-1}$ or higher (2). It has also been stated by the World Health Organization that certain subjects in the population may be particularly sensitive to possible allergic or immunotoxic effects. Dose-response studies for groups of such individuals are, however, not available (1).

In conclusion, many studies have clearly shown a relation between U-Hg on the one hand and effects

on the central nervous system and the kidneys on the other. The quantitative relations are still disputed, but biological exposure limits of 50 (33) and 35 (34) $\mu\text{g} \cdot \text{g creatinine}^{-1}$ (28 and 20 $\text{nmol} \cdot \text{mol creatinine}^{-1}$) have been proposed. Thus biological monitoring is suitable for assessing the risk of adverse effects and implementing measures to prevent such effects in exposed individuals.

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