Recommendation from the Scientific Committee on Occupational Exposure Limits for elemental mercury and inorganic divalent mercury compounds

8 hour TWA :	0.02 mg mercury/m^3
STEL (15mins):	-
Biological limit values (BLV):	10 µg Hg/l blood; 30 µg Hg/g creatinine in urine
Additional classification:	-

SUBSTANCE

This document covers elemental mercury and its inorganic divalent compounds. It does not include inorganic monovalent compounds or organic mercury compounds.

Identity and Properties

Chemical Name	Empirical Formula	Cas No.
Mercury (metal)	Hg	7439-97-6
Classification:	T; R23, Toxic by inhalation R33 Danger of cumulative effects N; R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.	
Mercuric oxide	HgO	21908-53-2
Mercuric chloride	$HgCl_2$	7487-94-7
	Classification: T+; R28 Very toxic if swallowed. T; R48/24/25 Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed C; R34 Causes burns N; R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	

Elemental mercury is a heavy silvery white liquid (SG 13.59 at 20°C), melting point -39°C and boiling point 356°C. It has a uniform volume of expansion over its entire

liquid range and low electrical resistivity. Mercury has a high vapour pressure; saturated air at 20°C contains 14 mg/m^3 which increases to 2400 mg/m^3 at 100°C. It readily forms amalgams with most metals.

Inorganic mercury compounds exist in two oxidation states, + 1 mercurous and + 2 mercuric; mercurous ions usually occur as dimers (Hg_2^{2+}). Only the divalent mercuric form is considered in this assessment. Mercuric chloride is readily soluble in water.

OCCURRENCE/USE

Mercury occurs naturally as sulphide. It is produced from the roasting of Cinnabar ore, which contains about 0.5% mercury. The only EU producer is the Almadén mercury mine in Spain. Other sources of mercury include Russia and China. The largest-scale use of mercury is in the chloralkali industry; elemental mercury forms a flowing cathode in cells used for the electrolysis of brine. Chlorine is formed at the anode and alkali metal amalgam at the cathode. The amalgam is hydrolysed to produce hydroxide and the mercury recycled to the electrolysis cells. Elemental mercury is also widely used in temperature and pressure measuring instruments and instruments used in control equipments. Electrical applications include manufacture of fluorescent and mercury discharge lamps. Amalgams with other metals are used in dentistry. Mercury is the raw material for preparation of mercuric compounds, principally mercuric chloride and mercuric oxide (IPCS, 1991).

HEALTH EFFECTS

Elemental mercury, as a vapour, is very well absorbed through the respiratory tract (Hayes and Rothstein, 1964); no such information is available for divalent mercury compounds. Absorption from the gastrointestinal tract is considerably less extensive for elemental mercury and is very poor for divalent mercury compounds (Bornmann et al, 1970). A small amount of skin absorption occurs on exposure to mercury vapour; the extent of skin absorption of divalent mercury compounds is unclear (Wunscher et al, 1991).

Once absorbed, both elemental and ionic mercury are widely distributed, it accumulates particularly in the kidney (Hayes and Rothstein, 1964). There is also passage to the foetus, particularly for elemental mercury (Clarkson et al, 1972). Elemental and divalent mercury undergo oxidation-reduction interconversions within the body; due to its lipophilicity, the elemental form is much more able to cross cell membranes. Excretion of mercury via urine, faeces and exhaled air is relatively slow, indicative of bio-accumulation on repetitive exposure (Rothstein and Hayes, 1964).

Biological monitoring of mercury exposure by untimed, random urine measurements is well established (DFG 2000). Urine mercury levels reflect average exposure over the previous few months in those chronically exposed. Blood mercury measurements are less frequently used due to their invasive nature and their reflection of only recent exposure (days). Their use has been confined to acute accidental exposure. There have been a number of reports allowing calculation of the ratios between airborne and urinary mercury levels or between airborne and blood mercury levels either by comparison of means or by regression techniques. Restricting analysis to those studies using personal atmospheric sampling a mean ratio of 1:1.4 for air to urine (mg/m^3 : mg/l) was derived. The individual ratios varied between 1:2.3 and 1:0.7. The mean ratio of air to blood (mg/m^3 : mg/l) was 1:0.48, varying between 1:0.17 and 1:0.81. (Aresini et al. 1995; HSE, 1995).

The acute toxicity of elemental or divalent mercury points to the kidneys and the central nervous system as target organs. Inhalation of 29 mg/m^3 of elemental mercury vapour for 1 hour produced kidney and brain damage in rabbits (Ashe et al, 1953). A single oral dose of 15 mg $HgCl_2.kg^1$ produced kidney damage in rodents (Svendsen et al, 1989).

No studies are available investigating skin or eye irritation, or the skin sensitisation potential of elemental mercury or divalent mercury compounds in animals. Elemental mercury vapour has produced both non-allergic and allergic dermatitis reactions in exposed humans. Divalent mercury compounds have been reported to produce skin sensitisation in humans (Ancona et al, 1982; De La Cuadra et al, 1990). No information is available on the eye irritancy of elemental mercury or the skin or eye irritancy of divalent mercury compounds in humans. There are no reports of respiratory sensitisation following exposure to either form of mercury.

In repeated exposure studies in animals, inhalation of elemental mercury vapour produced predominantly kidney and central nervous system toxicity, this being seen in rabbits at 0.86 mg/m^3 and in rats at 3 mg/m^3. In one study, no adverse effects were reported in several species at 0.1 mg/m^3, the only exposure level used in this study (Ashe et al, 1953). No data are available on the effects of repeated inhalation exposure to divalent mercury compounds in animals. For repeated oral exposure to divalent mercury compounds, a no observed adverse effect level (NOAEL) of 0.3 mg $HgCl_2$/kg was reported in rats, the most susceptible species studied (NTP, 1991). No repeated dermal exposure studies in animals are available.

The effects of repeated exposure to elemental mercury and divalent mercury compounds in humans have been thoroughly investigated. The majority of studies have sought to correlate the health state with mercury levels in blood and/or urine, and do not present reliable personal airborne exposure data. Psychomotor effects (motor speed and precision) indicative of central nervous system toxicity have been reported associated with mercury levels above 20 $mmol*mol^{-1}$ creatinine (35 µg/g creatinine) in the urine and 45 nM (9 µg Hg/liter) in the blood (Roels et al, 1985; Williamson et al, 1982; Piikivi et al, 1984). This urinary concentration appears also as a NOAEL for renal toxicity which is indicated by elevated protein marker levels in the urine; elevations of markers seen at higher mercury concentrations (*e.g.*, 50 µg/g creatinine and above) point to the beginning of manifest kidney toxicity. (Roels et al, 1985; Buchet et al, 1980; Roels et al, 1982).

Recently, Meyer-Baron et al. (2002) have performed a meta-analysis of published studies on neurobehavioural functions in occupationally exposed individuals, including those cited above. Out of a total of 44 studies, 12 studies were included in this analysis. The results were based on a total of 686 exposed and 579 control subjects. Mean effect sizes for 20 different neurobehabioural tests were calculated. Below mean urinary concentrations of 35 µg/g creatinine nine significant effect sizes were noted. Most of these appeared at urinary excretions between 22 and 29 µg/g creatinine, two effects at 18 and 19 µg/g creatinine and two at 34 µg/g creatinine. In the interpretation of the relevance of these data, it cannot be excluded that higher exposures in the working past might have been the reason for some of these effects at very low concentrations. Predominantly, the functional impairments referred to attention, memory and psychomotor functions, whereas those for memory and psychomotor functions proved as significant dose-response relationships between Hg in urine and effect sizes. The slight impairments of attention, memory and psychomotor functions may be compared to changes based on other variables, such as aging. The effect sizes described in the meta-analysis of Meyer-Baron et al. (2002) as measurable differences between exposed

and non-exposed subjects are comparable in their strength to steps in age norms of the respective tests between 5 and 20 years. Taking into account the percentages of mean performances these differences correspond to about 5 – 7% of decrease in performance. However, the large range of variability of study results, especially in the low dose range and at the background with no additional occupational exposure, must be stressed which questions the adverse nature of the isolated effects that are observed at low doses.

A subsequent evaluation of new neurobehavioural test results was performed with the result that in the total range up to 60 µg/g creatinine also isolated negative effect sizes were recorded, despite the fact that the majority of effect sizes was positive. A threshold of a lowest effect level could not be defined (Meyer-Baron, 2004). The authors concluded that their meta-analysis provided notable evidence for neurobehavioural impairments due to occupational mercury exposure at low concentrations.

In total, the overall data support the view that adverse effects on the central nervous system appear consistently with urinary mercury levels above 35 mg Hg/g creatinine (20 µmol/mol creatinine) which could be regarded as apparent threshold for such effects (IPCS 1991, HSE 1995).

No mutagenicity data are available for elemental mercury. Divalent mercury is clastogenic in mammalian cells *in vitro (Schoeny 1996).* However, although its mutagenicity *in vivo* has not been comprehensively explored, the available studies provide no evidence of mutagenic activity. On the chromosomal level, $HgCl_2$ produces aneugenic and clastogenic effects, as demonstrated in V79 cells in vitro (Thier et al. 2003). In a cell-free system investigating the gliding velocity of microtubules along immobilised kinesin, $HgCl_2$ affected the kinesin motor protein function in a dose-dependent manner; this was viewed along with the aneugenic effects of divalent mercury (Thier et al. 2003). Such effects are seen to go along with a practical threshold (Kirsch-Volders et al. 2003).

Although several studies of mutagenicity in humans have been performed, the variable quality and results obtained has produced no clear picture for either elemental or divalent mercury (HSE , 1995).

It has been concluded (Schoeny 1996) that data for clastogenicity in the absence of mutagenicity supported the view that inorganic mercury, if any, would produce carcinogenic effects only at very high and toxic doses.

EPA (1997) has evaluated the carcinogenicity of elemental mercury and inorganic mercury (Hg^{2+}). For elemental mercury it was outlined that human epidemiological studies failed to show correlation between exposure to elemental mercury vapour and increased cancer incidence, but the studies are limited by confounding factors. Only one study in animals had been reported (Druckrey et al. 1957); tumours were found only at contact sites, and the study is incompletely reported as to controls and statistics. These animal data were considered inadequate. It was concluded that Hg^0 was not classified as to carcinogenicity.

The carcinogenicity of mercuric chloride, via the oral route, has been investigated in rats and mice (NTP, 1991). EPA (1997) concluded that there were no data in humans linking mercuric chloride with carcinogenic effects and that data in animals were limited. Focal hyperplasia and squamous cell papillomas of the forestomach as well as thyroid follicular adenomas and carcinomas were observed in male rats gavaged with mercuric chloride (NTP 1991). In the same study, evidence for increased incidence of squamous

forestomach papillomas in female rats and renal adenomas and carcinomas in male mice were considered equivocal. All increased tumor incidences were observed at what were considered high doses (in excess of the MTD). In this context, the revelance of the thyroid tumour to human health evaluation has been questioned; these tumours are considered to be secondary to the hyperplastic response.

In 1993, a Working Group convened by the International Agency for Research on Cancer examined all the relevant literature and concluded that there was inadequate evidence in humans for the carcinogenicity of "mercury and mercury compounds" (*IARC, 1993*). Subsequently, a mortality study, 1950-1992, in the fur hat industry in Tuscany, Italy showed a statistically significant increase of stomach cancer in both male and female workers and of lung cancer in female workers receiving compensation for disease related to their occupational exposure to inorganic mercury. The stomach cancer excess was deemed to be related to study area characteristics rather than occupational exposure, whereas the nearly twofold lung cancer increase in women (11 deaths observed) could not be solely interpreted in terms of bias or confounding factors (*Merler et al. 1994*). A large cohort of more than 7,000 mercury miners and millers from Spain, Slovenia, Italy and Ukraine was followed up for cancer occurrence between 1950's and 1990's. Exposure to inorganic mercury was quantitatively estimated on the basis of environmental and biological monitoring data. Lung cancer was found to be increased in Slovenia and Ukraine only, and was not associated with duration of employment and estimated mercury exposure, although a trend with time since first employment was suggested. Also liver cancer was increased, especially among workers from Italy and Slovenia and among millers. Liver cancer occurrence showed a trend according to estimated cumulative exposure but not with duration of employment. In addition, the cancer incidence analysis in the Slovenian cohort confirmed the excess risk from lung cancer but not from liver cancer (*Boffetta et al. 1998)*. No definite conclusion can be drawn from the available findings.

The effects of elemental or divalent mercury on reproduction in animals have been poorly explored. No worthwhile experimental fertility studies are available. Developmental toxicity (reduced foetal weight and increased resorptions) was produced in rodents exposed to elemental mercury vapour at maternally toxic doses (above 0.2 mg/m^3), but not at maternally sub-toxic doses (Rao et al, 1982). The developmental toxicity of divalent mercury compounds by relevant routes of exposure has not been investigated in animals.

Most of the studies of reproductive outcome in humans exposed to elemental mercury have yielded negative results (HSE, 1995). Some data are available on reproductive function in humans exposed to divalent mercury compounds. (The information available on reproductive and developmental effects is compiled in the Appendix (Annexe 1).

RECOMMENDATION

A common OEL could be derived for elemental and divalent inorganic mercury, based on the interchangeability of individual chemical forms of mercury and the existing toxicological data base for any single species.

The available animal data on the effects of repeated inhalation of elemental mercury vapour indicate a NOAEL for systemic and developmental effects of about 0.1-0.2 mg/m^3.

There are substantial data from human studies on the two toxic effects of principal

concern *i.e.*, central nervous system toxicity and kidney damage. Much of the information correlates the health state with biological, rather than atmospheric monitoring of mercury exposure. There is common agreement (see above) that consistent central nervous system and kidney effects of adverse nature start to appear with urinary mercury levels above 20 mmol/mol (35 µg/g) creatinine, which is being viewed as apparent threshold for such effects.

However, recent meta-analytical data point to the possibility of beginning human neurobehavioral toxicity even below these limits, in a range of an excretion between 20 and 30µg Hg/g creatinine. But the representativeness of the exposure data in most available studies is a possible critical issue. Taking into account the percentages of mean performances, the differences in effects between exposed and non-exposed subjects are comparable in their strength to steps in age norms of the tests between 5 and 20 years and correspond to about 5-7 percent of performance decrease. Assuming that higher working exposures in the past might be the reason for the effects measured in some studies, a critical level of 30 µg Hg/g creatinine can be recommended to avoid possible behavioural effects.

This level is far from the percentiles 50 and 95 (0.4 and 2.2 µg/g creatinine in Germany) of the unexposed population and far from the mean level in urine of adults (1.45 µg/g creatinine in Germany) associated with > 10 dental amalgam fillings (UBA 2002).

Extrapolation from biological monitoring values to airborne exposure concentrations is subject to several qualifying conditions. Using the mean value for extrapolating from urinary mercury (µg/m3) of 0.7 (see above), a value of 35µg Hg/g creatinine is predicted to be equivalent to an airborne level of 25 µg/m3. Using a similar approach for extrapolating from blood measurements to air (see above), the alleged threshold of 45 nMHg in the blood equates an airborne level of about 20 µg/m3. However, the ratio between levels of airborne exposures to mercury and levels in biological materials may vary with workplace conditions (Bender et al. 2006). This underlines that the biological monitoring of mercury exposures is superior to air monitoring, as it is more closely related to health effects.

Taking all available data together and considering the “preferred value approach”, an exposure level of 0.02 mg/m3 (8-hour TWA) is considered to meet the criteria for a health-based OEL.

Biological limit values (BLV) are set to 10 µg Hg/l blood and to a urine concentration of 30 µg Hg/g creatinine.

In view of the cumulative toxicokinetic patterns of Hg no specific short-term exposure limit (STEL) is required.

Although some absorption of these forms of mercury into the skin is indicated, the potential contribution to systemic body burden seems to be insufficient to merit application of the "skin" notation.

The present evaluation is basically consistent with that produced by IPCS (1991) and HSE (1995).

At the levels recommended, no measurement difficulties are foreseen.

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Elemental Mercury and inorganic salts

Reproductive and developmental effects

The effects of *elemental mercury* on the male fertility in exposed workers was studied by Lauwerys et al. (1985), Alcser et al. (1989); They did not find an effect of the men's exposure to mercury on the fertility, or on miscarriages or congenital malformations. Cordier et al. (1991) found an significantly increased number of spontaneous abortions in wives of men exposed to elemental urinary with mercury levels of more then 50 `µg/L. Although mercury can be detected in semen, there seems to be no relation with male fertility (Hanf et al. (1996); Leung et al. 2001). A correlation between blood or urinary levels of mercury up to 103 µg/g creat. and the male gonadotropic hormones could not be found (Erfuth et al ,1990 and McGregor et al. 1991).

Studies on mercury exposed women show a more diverse outcome. Accidental exposure to high or mostly to unknown levels of mercury in the pregnant mother, mostly with maternal toxicity symptoms, can provoke adverse pregnancy outcomes. Epidemiological studies were performed in mercury exposed women by Heidam et al.. (1984), Brodsky et al. (1985), Ericson et al (1988)). In most of the studies the mercury exposure was not determined or low and no significant effects as spontaneous abortions, stillbirth or congenital malformations could be found. No reproductive effects were found in women occupational exposed to metallic mercury (46 cases) compared to the control group (19 controls) and also in the high exposed group (> 100 µg/m^3) compared to the low exposed group (< 100 µg/m^3) (Elghany et al. 1997). There are a few studies with positive results in smaller groups of exposed female workers. De Rosis et al. (1985) found some adverse effects in a small group of women working in a mercury vapour lamp factory with past mercury exposure to more then 50 µg/m^3 (menstrual cycle disorders, primary subfecundity) but other factors could not be excluded. In a similar study Sikorski et al.(1987) evaluated the reproductive outcomes in a small group of dental professionals (81 cases versus 34 controls) and found increased spontaneous abortions, stillbirths, congenital malformations in the exposed group, but there were serious shortcomings in evaluation of the exposure to mercury in de exposed group. A lot of attention was given to studies in female dental workers, who can combine occupational exposure with their own dental amalgam restorations. Dahl et al. (1999) examined the mercury exposure in dental surgeries on the basis of reported use of dental materials and techniques in relation to the fertility of 558 female dental surgeons. The estimated urinary mercury concentration was 10-25µg/L for 50 or more amalgam fillings a week. Fecundability ratios (based on time to pregnancy) were determined in the exposed groups and in a control group of high school teachers. Not only the mercury exposure but also other chemical and physical risk factors were examined. No significant differences were found in fertility between the dental surgeons and the high school teachers and there was no effect of the mercury and other chemical exposure within the group of dental surgeons.

Developmental effects were examined in animals by inhalation exposure in rats by Baranski et al. (1973), with effects on the foetal outcome, but at concentrations at which maternal toxicity can occur. Frederikson et al. (1992) found behavioral changes in rats with early postnatal exposure. Danielson et al. found learning difficulties in the offspring of the high exposed group during gestation. Newland et al. (1996) found

behavioral instability in treated squirrel monkeys. The exposure levels ranged from 50 to 1800`µg/m^3. (1993).

For *inorganic mercury* there have been some case studies with spontaneous abortion after ingestion of mercuric chloride (30 mg/kg/day) (Alfonso et al. 1960) and other not well documented cases reported by Schardein (1993). Animal studies were mostly with mercuric chloride, some with mercuric nitrate and mercuric acetate. Lee et al. (1975) found a significantly lower fertility after IP injection of a single dose of mercuric chloride. Chowdury et al. (1985) found inhibition of hormone synthesis in male rats at 50 µg/kg and testicular changes in different animal species from 5 mg/kg i. p. At this levels general toxicity is possible. Effects on female mice fertility after SC injection of mercuric nitrate were seen by Lach et al. (1972). A lot of studies focused on the developmental toxicity by exposing pregnant animals to mercuric chloride, by inhalation, orally or by SC or IP injection. Different effects as resorptions, decreased fetal weight and abnormal fetal development were observed. Most of these studies do not provide appropriate data due to the high doses used and the presence of maternal toxicity effects (EPA 1997).

Conclusion on reproductive and developmental effects of elemental mercury

For elemental mercury there are indications that mercury can be found in the semen of exposed men but there is no correlation with male infertility. Studies of paternal exposure to mercury on abortion in their wives are mostly negative. The studies on exposed female workers give no clear evidence of any effect. The studies wit positive effect positive (Cordier et al. and De Rosis et al.) have too much weaknesses to allow a clear conclusion. The available animal data on developmental effects are suggestive for some effects at rather higher concentrations. According to the present criteria documents there are insufficient data for a NOAEL of mercury for these effects. It is expected that this value should be higher then for the kidney and the central nervous system effects (HSE criteria document 1995).

Conclusions on reproductive and developmental effects of inorganic mercury

The data available from animal experiments are mostly related to mercuric chloride and show effects at higher doses, which can cause maternal toxicity. These data are insufficient to indicate an NOAEL for inorganic mercury salts.

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