Mercury and inorganic mercury compounds

Supplement 2011	
MAK value (2010)	**0.02 mg/m³ (calculated as Hg)**
Peak limitation (2002)	**Category II, excursion factor 8**
Absorption through the skin (2010)	**H**
Sensitization (1999)	**Sh**
Carcinogenicity (1999)	**Category 3B**
Prenatal toxicity (2010)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value (2007)	**25 µg mercury/g creatinine**

The 1980 documentation on "mercury" (see Documentation "Quecksilber", 1981, only available in German) and the 1999 and 2002 supplements on "mercury and inorganic mercury compounds" (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German) (see Supplement, "Mercury and inorganic mercury", 2002, only available in German) as well as the 1997 documentation of the BAT value (100 µg mercury/L urine) (see Documentation "Mercury, metallic mercury and inorganic mercury compounds" 1998) and the supplements of 2005 (30 µg mercury/L urine) (see Supplement "Mercury and its anorganic compounds", 2006, only available in German) and 2009 a, b (25 µg mercury/g creatinine) (see Addendum, "Quecksilber und seine anorganischen Verbindungen", 2009 a, only available in German and Addendum, "Quecksilber und seine anorganischen Verbindungen", 2009 b, only available in German) are already available. This supplement will examine whether the MAK value must be adjusted, after considering the reduction of the BAT value. In it, assessment-relevant investigations on other endpoints, especially on reproductive toxicity, will also be amended.

Metallic mercury is used in thermometers, manometers, mercury vapour lamps, energy-saving lamps and special batteries as well as in metal production. It is also contained in amalgams. Organic and inorganic mercury compounds are used as

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fungicides and insecticides, and for the treatment of crop seed, wood and animal hair.

Substance	CAS number	Molecular weight [g/mol]	Formula
Metallic mercury	7439-97-6	200.59	Hg
Mercury(I)chloride	10112-91-1	472.09	Hg_2Cl_2
Mercury(II)chloride	7487-94-7	271.52	$HgCl_2$
Mercury cyanate (mercury fulminate)	628-86-4	284.62	$Hg(CNO)_2$
Mercury(II)nitrate	10045-94-0	324.66	$Hg(NO_3)_2$

1 Toxic Effects and Mode of Action

At the workplace, most exposure is to mercury vapour. Exposures to dusts with inorganic mercury compounds are very rare. The main effect of short-term exposure to high concentrations of mercury vapour is lung damage; ingestion of mercury(II) compounds mainly leads to gastrointestinal and renal damage. The central nervous system is the target organ after long-term exposure of humans to mercury vapours. Characteristic forms of tremor are followed by psychic and neurological changes ("mercury erethism"). The kidney is the most sensitive target organ after oral intake of mercury(II) chloride in animal studies.

In a carcinogenicity study with male mice, mercury produced renal adenomas and carcinomas of unknown relevance for humans. In in vitro genotoxicity tests, inorganic mercury compounds are clastogenic at high doses. No genotoxic effects were found in in vivo tests.

Mercury and its inorganic compounds are absorbed through the skin and cause sensitization of the skin. No investigations are available on their potential for respiratory sensitization.

The most sensitive endpoints for the offspring seem to be foetal mortality, postnatal mortality and behavioural changes. Epidemiological studies yielded no consistent results. In a number of studies where women were exposed to mercury during pregnancy, an increased number of abortions and malformations were reported, although this effect did not appear in other studies. In animal experiments with inhalation of mercury vapour, no skeletal or visceral examinations were performed; as a result, the data obtained permit no conclusive assessment.

2 Mechanism of Action

The biological activity of divalent mercury ions is determined essentially by their high affinity for thiol groups. Binding of the ions to the thiol groups of proteins can result in impairment of a multiplicity of functions. All the biological and toxicological effects of exposure to elemental mercury are put down to the action of mercury ions. The chains of reactions which begin with the binding to thiol groups and result in cell damage or diseases of the organism have been described in numerous hypotheses based on more or less adequate experimental data (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German); Tan et al. 2009).

Causes for impaired male fertility could be: inhibited enzymes, a reduced testosterone concentration, inhibition of the function of mitochondria or microtubules or inhibition of DNA, RNA and protein synthesis. Mercury also activates oestrogen receptors. Knockout mice in which the oestrogen receptor α was absent, were infertile, but where the oestrogen receptor β was absent, fertility was retained. Sometimes an effect on female fertility was also observed; the mechanism of this is not clear, however (Tan et al. 2009).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Elemental mercury

Inhalation and oral absorption

Approximately 80% of inhaled mercury vapour is absorbed via the lungs. Due to its high fat solubility, it rapidly penetrates the alveolar membrane. Metallic mercury is practically not absorbed via the gastrointestinal tract. In rats, absorption was below 0.01% of the amount ingested (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

Exposure of rats to mercury vapour during pregnancy produced in their offspring an accumulation in the cerebellum, hippocampus and other areas of the nervous system responsible for motor functions and learning (Newland et al. 1996). When pregnant guinea pigs were exposed, the mercury concentration in most organs of the foetuses was far below that in the dams; it was higher in the liver only. During postnatal development, a redistribution of the mercury into the kidneys and the brain took place (Yoshida 2002). When mice were exposed to mercury vapour at the end of pregnancy, the foetuses were found to have more mercury in the kidneys than in the liver or brain. After exposure of pregnant metallothionein knock-out mice, the accumulation of mercury in the foetuses was higher than in the wild type

animals, in which metallothionein had been expressed in the brain. As for the accumulation of mercury in the placenta there was no difference between metallothionein knock-out and wild type animals (US EPA 2007; Yoshida 2002).

In the blood, mercury is largely bound to the erythrocytes where, in the presence of hydrogen peroxide, it may be oxidized by the action of catalase to divalent mercury and bound, for example, to intracellular or extracellular sulfhydryl groups. The fate of the oxidized mercury is like that of an ingested mercury salt (see below). As the enzymatic oxidation of mercury is saturable, the proportion of the mercury dissolved in plasma which is in the metallic form increases with increasing dose. Because metallic mercury is lipophilic and readily diffusible, it is distributed in body fluids, cells and organs and also crosses the blood-brain barrier to enter the brain where it can also be oxidized. As divalent mercury crosses the blood-brain barrier only in very small amounts, the ion accumulates after exposure to elemental mercury in the brain, presumably in complexes with thiol groups or other ligands (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

The elimination of metallic mercury bound to the blood takes place mainly by exhalation through the lungs with an elimination half-life of about 18 hours. During and immediately after brief exposures to mercury vapour, metallic mercury can also be detected in the urine, faeces, saliva and perspiration (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

In workers in chloralkali plants, a correlation between absorption via inhalation and urinary excretion of mercury was established. There were wide variations in ambient air measurement and biological monitoring results determined in individuals as well as significant differences between the values of various workers at the same workplace. Determining the exposure of a person to mercury is therefore only useful when personal biomonitoring is applied (Bender et al. 2006).

Absorption through the skin

The absorption of mercury vapour through the skin was investigated in five volunteers who held their right hands in an airbag containing ^{203}Hg vapour for 27 to 43 minutes. The concentration range was 0.88–2.14 ng/cm^3 (corresponding to mg/m^3). The radioactivity of the exposed hand surface was measured before and directly after exposure and up to 60 days after exposure. After correction of the radioactivity values with the radiation count values of the left hand and the whole-body background, the absorption of mercury via the hand surface was calculated. Between 216 and 844 ng mercury were absorbed through the skin. Skin flux values of 0.0101–0.0402 ng Hg/cm^2/min per ng Hg/cm^3 (Hursh et al. 1989) were obtained. This corresponds to 0.606–2.412 ng Hg/cm^2/hour per mg Hg/m^3 or an uptake of 87–347 µg Hg per mg Hg/m^3 in relation to the whole body surface (18 000 cm^2) and an 8-hour working day. The authors compared the dermal absorption of mercury with that after inhalation at an air concentration of 50 µg/m^3 (TLV value valid at that time). They assumed a respiratory volume of 10 m^3 during the shift and a

pulmonary retention of 80%. In calculating the absorption through the skin they used the mean absorption value of 0.024 ng Hg/cm²/min per mg Hg/m³ obtained in the study, and assumed a whole body surface of 18 000 cm². From this comparison, it was found that the uptake through the skin corresponded to 2.6% of the amount absorbed via the lungs.

The percutaneous absorption of mercury vapour was also investigated in 6-week-old male Wistar rats. Their tails were exposed to a mercury vapour concentration of 1.1 mg/m³ for six hours a day on five days per week for four weeks. After exposure, the amounts of mercury in heart, kidneys, liver, brain and in blood were determined and compared with those in a control group. At the end of the experiment, the exposed animals showed higher amounts of mercury than the control animals in the kidneys only. No mercury uptake rate could be determined from this experiment (Wünscher et al. 1991).

Inorganic mercury compounds

Inhalation and oral absorption

The few available studies indicate that inorganic mercury compounds inhaled in the form of aerosols or dusts are absorbed via the lungs; there are, however, no quantitative data for this absorption. In the gastrointestinal tract, 7% to 15% of an ingested dose of mercury(II) compounds is absorbed; the amount absorbed correlates with the solubility of the compound in water (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

In the blood, the divalent mercury ion binds to the sulfhydryl groups of plasma constituents and erythrocyte proteins. The ion accumulates in the liver and kidney, predominantly in the latter. After exposure for longer periods, up to 90% of the total mercury in the organism is found in the kidneys, mostly in the proximal tubules. The mercury ions are probably mostly bound to metallothionein, a heavy-metal-binding protein which can be induced by mercury. Unlike metallic mercury, the divalent mercury ion cannot readily cross the blood-brain barrier. Animal studies have demonstrated that the mercury levels in the brains of animals exposed to elemental mercury are about 10 times those found in animals treated with similar body burdens of divalent mercury (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

The mercury concentration in the placental blood is about 70% higher than in maternal serum (Tan et al. 2009).

Divalent mercury is eliminated via the kidneys and the intestine. Volunteers given mercury nitrate by intravenous injection excreted between 6.3% and 35% of the dose with the urine and between 17.9% and 38.1% with the faeces within 70 days. The half-life for total mercury in the organism was estimated to be about 58 days. For individual compartments, the values deviated markedly from this estimate. Thus the biological half-life of mercury in the brain can be several

years (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

The half-life of mercury chloride in the testes of mice after intraperitoneal injection of 1 mg Hg^{2+}/kg body weight was 55.5 days. The amount absorbed was greatest in the late elongated spermatids (Lee and Dixon 1975).

Absorption through the skin

In guinea pigs, 2% to 3% of the applied mercury(II) chloride amount is absorbed through the skin within five hours (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

In in vivo penetration studies, sealed glass cylinders 2 cm in diameter with various concentrations of radioactively labelled mercury(II) chloride ($^{203}HgCl_2$; 1 ml volume; 8 mg Hg/ml and 16 mg Hg/ml; corresponding to dermal applications of 2.55 mg/cm² and 5.1 mg/cm²) were attached to the abdominal skin of guinea pigs. Penetration was measured by the decrease in radioactive disintegration rate at the site of application (Friberg et al. 1961; Skog and Wahlberg 1962). In the study by Friberg et al. (1961), 3.3% (at 8 mg Hg/ml) and 4.5% (at 16 mg Hg/ml) of the amount applied were absorbed within five hours. Considering the applied quantities of 2.55 mg/cm² and 5.1 mg/cm², this corresponds to flux values of 17 µg Hg/cm² and hour or 46 µg Hg/cm² and hour, respectively. In the study by Skog and Wahlberg (1962), 3.0% (at 8 mg Hg/ml) or 3.6% (at 16 mg Hg/ml) of the applied amount was absorbed under the same conditions. These values correspond to flux values of 15 µg Hg/cm² and hour or 37 µg Hg/cm² and hour, respectively. The results of both studies indicate a positive relationship between the amount applied and the amount absorbed through the skin.

In a flow-through diffusion cell with a penetration area of 0.95 cm², the penetration of mercury(II) chloride through the human skin was investigated. The acceptor solution was a physiological saline solution to which 6% PEG-20 oleyl ether and gentamycin sulfate were added. The dosing phase consisted of a ^{203}Hg-containing buffer solution (20 µl) on the one hand and a ^{203}Hg-containing soil matrix (40 mg) on the other. Whereas penetration of mercury through the human skin could be demonstrated after application of the aqueous solution, mercury was always below the detection limit where soil was used as matrix. With the lower dose at the site of application of 0.176 nmol/cm² (corresponding to 0.036 µg ^{203}Hg/cm², about 1.8 µg Hg/ml), a permeation coefficient (K_p) of 0.71 ± 0.14×10^{-3} cm per hour was determined, whereas at the higher dermal dose of 1.215 nmol/cm² (0.247 µg ^{203}Hg/cm², about 12 µg Hg/ml), a K_p value of 0.16 ± 0.016×10^{-3} cm per hour was determined. A large part (19–45%) was found in the skin after 72 hours (Sartorelli et al. 2002). From the percentage amount in the receptor phase after 24 hours (0.34%), a flux of 7 µg/2000 cm² and hour can be calculated for the higher concentration. From the solubility of 74 mg $HgCl_2$/ml water at 20°C and the Kp values, fluxes of 9–39 µg Hg/cm² and hour were obtained, i.e. 18–78 mg Hg/2000 cm² and hour for exposure to a saturated solution lasting one hour.

The dermal penetration of mercury was investigated in an ex vivo model with pig skin and flow-through diffusion cell with a penetration area of 0.64 cm^2 and with a $^{203}HgCl_2$-exposed soil matrix. The soil matrix was loaded with a concentration of 5.37 mg Hg/kg. Whereas a part of the soils was used directly after exposure for the penetration experiments, a second part was stored at room temperature for three months before the penetration test. 30 mg of the contaminated soils or 5 µl of an ethanolic ^{203}Hg solution were applied to the application area of the diffusion cells and the penetration of radioactive mercury recorded over a period of up to 16 hours. After the exposure, 66% of the applied mercury amount was absorbed in the experiment applying the Hg solution, 38–40% on application of the fresh soils and only 3% to 8% of the applied mercury amount with the aged soils (Skowronski et al. 2000). From these experiments, however, it also becomes clear that the major portion of the mercury taken up by the end of the exposure had been absorbed into the skin, but only a small part reached the acceptor phase during the experiment.

Summary: Volunteer studies showed that metallic mercury is also absorbed through the skin from the vapour phase. Compared with inhalation, the dermal uptake is, however, below 10%. From in vivo studies using aqueous mercury(II) chloride solutions in guinea pigs, an absorpion in the range of 15 to 46 µg Hg/cm^2 and hour can be derived. This corresponds to an absorbed amount in the range of 30 to 92 mg per 2000 cm^2 and hour. However, in vitro results with pig skin have shown that a major part of the mercury absorbed through the skin is stored within the skin, so that only a small part is assumed to be transiently systemically available.

3.2 Metabolism

Elemental mercury

Elemental mercury is almost completely oxidized to its divalent form in the blood and other tissues, and also eliminated in this form (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

Inorganic mercury compounds

After oral administration of mercury(II) salts, the exhalation of small quantities of elemental mercury could also be demonstrated in rats and mice. From this, it was concluded that divalent mercury in the organism can also be reduced to elemental mercury. In rats, methylation of divalent mercury by intestinal bacteria was observed (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German; Rowland et al. 1977). However, it seems that this does not occur in humans (Mosel et al. 2006).

In the body, mercury(I) compounds dissociate into elemental mercury and mercury(II) ions (US EPA 2007).

4 Effects in Humans

4.1 Single exposures

The inhalation of high concentrations of **mercury vapour** for example in an accident during gold production produced respiratory problems and chemical pneumonia (Shimada et al. 2004).

4.2 Repeated exposures

In the documentations of the MAK value from 1999 (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German) and the BAT value from 2005 (see Supplement "Mercury and its anorganic compounds", 2006, only available in German), it is shown that the most sensitive endpoints for repeated uptake of mercury and its inorganic compounds are nephrotoxicity and neurotoxicity. Evaluation of the comprehensive data for animals and humans showed that no nephrotoxic (taking into account the 95th percentile) or clinically relevant neurotoxic effects are to be expected in humans at a biological value of 30 µg mercury/L urine. In 2005, the BAT value for mercury of 100 µg/L urine was reduced to 30 µg/L urine (see Supplement "Mercury and its anorganic compounds", 2006, only available in German)) and converted to 25 µg mercury/g creatinine in 2007 when creatinine excretion was taken as reference (Addendum, "Quecksilber und seine anorganischen Verbindungen", 2009 a, only available in German and Addendum, "Quecksilber und seine anorganischen Verbindungen", 2009 b, only available in German). The following includes only those studies published since then, in which a determination of the internal exposure and a valid recording of effects were carried out.

In a cross-sectional study, 49 male workers at a chloralkali plant who had not been further exposed to mercury vapour in the last 5 years, behavioural functions were determined and compared with those of 49 male control persons (matched for age). The workers had been exposed on average for 13.1 years and had during this time a calculated mean urinary concentration of 9.3 nmol Hg/mmol creatinine and year (about 16.5 µg mercury/g creatinine). The workers' exposure had ended after an average of 4.8 years (range 4.2 to 10.0 years). Most persons (41 workers, 40 controls) had already been investigated five years previously, while they were still exposed. The neurobehavioural test scores and the number of subjective symptoms were similar in the previously exposed and the control persons. Also, no change in

these parameters was found in the previously exposed workers versus the results obtained five years previously. However, while the workers, were still exposed to mercury, they had concentration-dependent lower scores in the Digit Symbol Test, which was assessed as a slight effect. These parameters had improved in the persons with a high mercury concentration in blood five years after the end of exposure (Bast-Pettersen et al. 2005). Thus, this study revealed no effects in the exposed workers compared with controls.

No significant effects occurred in neurological investigations (tremor measurements with an accelerometer and a laser-based system) in 43 workers from chlor-alkali plants, who had been exposed to **mercury vapour** and had mercury concentrations of 1.3 to 25 µg/g creatinine. They were compared with 22 control persons of the same age, whose mercury concentrations were 0.2 to 4.1 µg/g creatinine (Wastensson et al. 2006).

In 27 mine workers and smelters, hand tremor and postural sway were measured and compared with the values from 52 non-exposed control persons. The geometric mean of the mercury content in urine was 228 µg/g creatinine in the workers and 2.6 µg/g creatinine in the control persons. Total tremor intensity and frequency-specific tremor intensities at 1-6 and 10-14 Hz were significantly larger in the exposed workers than in the unexposed, though they were not correlated with the urinary mercury concentrations. The postural sway parameters showed no differences between exposed and non-exposed persons. The test on transversal sway with eyes open was however, correlated with the urinary mercury concentration (Iwata et al. 2007). This study produced no clear quantitative association between mercury concentrations and effects.

In persons who had been occupationally exposed to **mercury** daily for at least five years in a dental clinic, exposure to mercury and its effects on the thymus hormone thymulin and on NO synthetase were investigated. The exposed group consisted of 15 male and 6 female dentists and 18 assistants. The matched control group consisted of 42 physicians and nurses from the hospital. The dentists always wore gloves and occasionally facemasks, though the nurses never wore protective clothing. Exposure was determined by occupational activities and medical history, and levels of mercury in urine and blood. These were 19.8 µg/g creatinine and 7.8 µg/L blood in the exposed persons and 5.4 µg/g creatinine and 4.8 µg/L blood in the controls, respectively. Thymulin was determined in blood (0.48 g/ml exposed; 0.80 g/ml non-exposed persons), nitrite (18.1 and 25.11 µmol/L, respectively), and nitrate (7.44 and 9.14 µmol/L, respectively) as marker for NO in serum. All three parameters were significantly reduced in the exposed persons. This correlation was more pronounced in the assistants than in the dentists (Farahat et al. 2009). As these findings are interpreted as indication of a possible immunosuppressive effect, but no immunosuppression has been demonstrated in other studies to date, the study is not used to derive a MAK value.

Workers in the gold industry, where the gold is recovered by **mercury** amalgamation, were exposed to 42.7 mg/m^3. The mercury concentration in blood was 79.1 µg/L while the glutathione peroxidase activity of the erythrocytes (49.32 mg/L)

was reduced compared with controls (68.54 mg/L) (Jayaprakash 2009). As no neurological investigations were carried out in this study, it is not used to derive a MAK value.

A case report describes the occurrence of membranous glomerulonephritis in a male metalworker who had worked for nine months in a whole-body protective suit with external air supply in a hall containing a running chloralkali electrolysis plant (no details on mercury concentration in the air). Prior to starting work, his mercury concentration in the blood was 1.2 µg/L, the urine was normal. Seven weeks after the onset of the disease, the mercury concentrations were 16.1 µg/L (blood) and 83 µg/L (urine). Contaminated or leaking air hoses or a not regularly worn breathing mask were suspected as possible causes for mercury exposure (Gier-Stuschke et al. 2006). As there was no correlation between external and internal exposure, this report is not used to derive a MAK value.

4.3 Local effects on skin and mucous membranes

After repeated exposure to **mercury vapour** or various mercury compounds, occasional acrodynia with desquamation of large scales of skin and scarlet skin discoloration ("pink disease") may develop, especially in children. The other reported symptoms include sleeplessness, irritability, perspiration, increased blood pressure and tachycardia. The pathogenesis of this disorder is not yet fully understood. Nor are any data available for a dose-response relationship (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

4.4 Allergenic effects

Sensitizing effects on the skin

In the early literature, eczematous reactions to mercury compounds were listed as common occupational diseases. Although it may be assumed that (skin) contact with mercury and mercury compounds is avoided nowadays as far as possible both at work and in the private sphere, the recent literature often contains case reports of allergic reactions and relatively frequent positive reactions in patch tests carried out with patients at clinics (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

Since the 1999 documentation, quite a number of further reports on sensitization and contact allergic reactions to mercury or inorganic mercury compounds have appeared. Thus, in 2004, in the hospitals of the Informationsverbund Dermatologischer Kliniken (Information Network of Departments of Dermatology; IVDK), a positive reaction was obtained in 3% of 8743 patients in tests with mercuric amidochloride (Oppel and Schnuch 2006). Between 1996 and 1999, 35 082 patients were tested with 1% mercuric amidochloride, with positive results in 871 of them

(2.5%) (Uter et al. 2002). Between September 1997 and December 2000, 8.9% of the 2766 consecutively tested patients in an Austrian study reacted to 0.5% mercury in petrolatum and only 0.9% of those tested to 5% amalgam in petrolatum (Wöhrl et al. 2003). Between 1978 and 2003 at a Taiwanese centre, 185 of 3559 patients (5.2%) reacted to mercuric amidochloride and 27 patients (2.5%) to mercury(II) chloride. About 45% of the reactions to mercuric amidochloride were considered to be clinically relevant either currently or previously (Cheng et al. 2008).

In children and young people, a relatively high frequency of sensitization to mercuricamidochloride is still found, which is partly within the range of rates for adults (for example a positive reaction in 2.2% of 234 children and youths (Czarnobilska et al. 2009), but which is also partly higher than in adults (for example Heine et al. 2004; Seidenari et al. 2005). Nevertheless, the German Contact Allergy Group does not recommend the routine testing of mercuric amidochloride with children (Worm et al. 2007). Of 923 female dental assistants in the Helsinki region, 107 employees were patch tested for a suspected occupational dermatosis. None of those tested showed a positive reaction to 20% amalgam in petrolatum (Alanko et al. 2004). In a Korean investigation, a positive reaction to mercuric amidochloride was found in 8 of 49 tested dental technicians (Lee et al. 2001).

In several case reports, a systemically mediated contact dermatitis ("baboon syndrome") is described which frequently occurred after re-exposure to Mercurochrome® or other antiseptics containing mercury following preceding sensitization. Examples for this are: Exposure to mercury vapours from broken barometers or manometers (Oh et al. 2003; Suzuki et al. 2000), the contact of a 15-year-old boy with mercury vapours in a cinnabar mine (Bartolome et al. 2000), the twice yearly "ritual" contact with mercury vapours in a single metal worker who had in the past frequently used Mercurochrom® (Özkaya 2008) or contact with mercury vapours from broken thermometers (Belhadjali et al. 2008; Garcia-Menaya et al. 2008; Wen et al. 2007). In other cases, systemic reactions were induced in a 12-year-old boy after "playing" with metallic mercury (Lerch and Bircher 2004) or also by contact with mercuric amidochloride in a "lead cream" (Özkaya et al. 2009).

In addition, further reports on sensitization and positive patch test reactions to mercury or mercuric amidochloride are available involving a relatively large number of patients with lichenoid changes of the oral mucosa (for example Athavale et al. 2003; Laeijendecker et al. 2004; Wong and Freeman 2003). The removal of amalgam fillings can result in healing or improvement of the symptoms in the majority of those affected (Dunsche et al. 2003 b; Laeijendecker et al. 2004; Pezelj-Ribaric et al. 2008). Compared with the lymphocytes of healthy control persons, however, the lymphocytes of patients with lichenoid changes of the oral mucosa showed no specific proliferation after stimulation with mercury(II) chloride (Loftenius et al. 1999).

On account of its low specificity, however, the lymphocyte transformation test is not considered suitable for diagnosing an allergy to mercury (Cederbrandt and Hultman 2000; Cederbrandt et al. 2000), and the tendency to high positive rates obtained in the modified lymphocyte transformation test (MELISA) (Valentine-

Thon and Schiwara 2003; Valentine-Thon et al. 2006) are not suitable for assessing its sensitization potential.

In studies on the polymorphism of gluthathione-S transferase T1 (GSTT1), a significantly higher frequency of the GSTT1-negative genotype was found in 5 of 9 patients with sensitization to phenyl mercury salts or mercuric amidochloride (compared with 27 of 169 healthy control persons) (Westphal et al. 2000).

Sensitizing effects on the airways

To date, there are no reports available on a possible sensitization of the airways.

4.5 Reproductive toxicity

Fertility

Male fertility

Based on a questionnaire analysis no impact of metallic **mercury vapour** on the fertility of male workers in zinc/mercury factories (n = 17), chloralkali plants (n = 35) or in the production of electrical accessories (n = 51) could be detected. The number of expected births was compared with the number of those actually born in the group of exposed workers and a matched control group. According to the questionnaire, none of the workers had been exposed to solvents, cadmium or lead. In the case of lead, this was reflected by a very low concentration in the urine. The concentration of mercury in the urine of the exposed workers was 5.1 to 272.1 µg/g creatinine (Lauwerys et al. 1985). The measurement of mercury in the urine was conducted during the questionnaire process, i.e. not at the time to which the information refers. This is why this study cannot be included in the assessment process.

The rate of spontaneous abortions in 152 women, whose husbands had been exposed to **mercury vapour** in a chloralkali plant was compared with a control group of 374 women at the same plant. The rate of abortions in the wives increased depending on the mercury content in the urine of exposed workers before pregnancy. At a mercury concentration of 50 µg/L urine, the risk of a spontaneous abortion was doubled (OR 2.26; 95% confidence interval: 0.99–5.23). Associations between the reported abortions and known risk factors were not found (Cordier et al. 1991). Confounders such as smoking or alcohol consumption were, however, not taken into account. Therefore, from this study, no causal relationship between the mercury exposure of men and abortions in their wives can be deduced (Health Council Netherlands 2000; Kahn et al. 2004).

Mercury concentrations in blood and urine were determined in male workers, who had been occupationally exposed to **mercury vapour** for an average of 4.5 years (range: 2 to 18 years) (7 workers at a chloralkali plant, 3 occupied in repairing

fluorescent tubes, one worker at a mercury refinery). The individual average serum concentration from all observations varied between 70 to 170 nmol Hg/L in the workers. For the refinery worker an average serum concentration of 275 nmol/L could be calculated for the last eight working years. From a few measurements during the first ten years an average twice as high might be assumed during that period. In the chloralkali workers, 90% of the values of the morning urine were within 25 to 50 nmol/mmol creatinine. In the refinery worker, the concentration in the urine over the preceding 18 months was on average 117 nmol/mmol creatinine (seven samples, range 34 to 195 nmol/mmol creatinine). The mean age of the group was 33 years (range 23 to 49), that of the control group of municipal workers without mercury exposure 32 years (range 24 to 39). No association was found between the increased mercury concentration in the blood and urine of the exposed persons and the concentrations of prolactin, testosterone, luteinizing hormone or follicle-stimulating hormone in serum (Erfurth et al. 1990).

In a group of nine male dentists who had been working on average for 28 years (range 25 to 30 years) and who had an average age of 57 years (range 55 to 62 years), the blood and urine concentrations of mercury and the hormone values were determined and compared with a control group of 11 municipal workers without mercury exposure having an average age of 57 years (range 51 to 62 years). No association between the increased mercury concentration in the blood and urine of the exposed persons and the concentrations of prolactin, testosterone, luteinizing hormone or follicle-stimulating hormone in serum was found (Erfurth et al. 1990).

In 80 men with an unfulfilled wish to have children, no correlation was found between the mercury concentration in the morning urine and the ejaculate and the number of amalgam fillings. The concentrations were low, in 75% of the cases they were below the detection limit of 5 µg/L ejaculate. Workers exposed occupationally to mercury with proven fertility had a clearly higher concentration of 10 to 65 µg/L ejaculate (Hanf et al. 1996).

In a retrospective cohort study with male workers at a plant belonging to the US Department of Energy in Michigan,USA, long-term exposure to **metallic mercury** (for at least 4 months) had no effect on the number of pregnancies in their female partners. The mercury concentration in urine was 2144 to 8572 µg/L. The number of miscarriages in the exposed group was already higher prior to exposure (WHO 2003; Health Council Netherlands 2000). An evaluation of a dose-response relationship is not possible on the basis of these data.

Female fertility

In 153 female workers at a factory producing mercury vapour lamps, **mercury vapour exposure** at the time of the study had been reduced from over 50 µg/m^3 to below 10 µg/m^3 and showed menstrual disorders and reduced primary fertility with increased frequency compared with a control group of 193 women at another factory belonging to the same company. Both groups were exposed to stress factors such as production noise and working in shifts. Exposures were recorded by means

of personal interviews. No clear association between the level of exposure concentrations at the factory and the effects on fertility could be found. This study can neither prove nor exclude the possibility that occupational exposure to this concentration of mercury has a negative effect on female reproduction (De Rosis et al. 1985). As exposure was recorded by personal interview and not by measurement, a defined concentration-response description is lacking.

Eighty-one female dentists and female dental assistants (aged 21 to 56 years) exposed occupationally to **metallic mercury** had complained more frequently of pain during menstruation than 34 non-exposed women (aged 20 to 46). In the exposed women, the mercury concentration was on average 0.517 mg/kg (controls 0.1 mg/kg) in the hairs of the scalp and 0.381 mg/kg (controls 0.06 mg/kg) in the pubic hairs (Sikorsky et al. 1987). An evaluation of a dose-response relationship is not possible on the basis of these data.

In female dentists and dental assistants or female technicians, occupational exposure to **metallic mercury** had no effect on the spontaneous rate of abortions (Ericson and Källén 1989). Data on exposure concentrations or internal exposure are lacking.

In 296 dental assistants performing more than 30 **amalgam fillings** per week under poor hygienic conditions, fecundability was 63% (95% CI: 42–96%) compared with the non-exposed control group. When only a few amalgam fillings were carried out under good hygienic conditions, women were more fertile, than the unexposed controls (in which other factors influencing fertility were suspected) (Rowland 1992; Rowland et al. 1994). The usefulness of this investigation was questioned due to the reduced fertility in the control group (Health Council Netherlands 2000).

It has been reported that **mercury chloride** correlates with spontaneous abortions, but no details are provided in two investigations (no other details; Health Council Netherlands 2000).

The number of **amalgam fillings** in the teeth of pregnant women was directly associated with the mercury concentration in the hair of newborn, but not with that in the amniotic fluid. The birth weight of children from mothers with a greater number of amalgam fillings was not significantly different than those with only a few amalgam fillings (US EPA 2007).

The number of miscarriages was correlated with the concentration of **total mercury** in well water. In a study with women from Iowa, a correlation between total blood mercury concentration and stillborn or children with defects at birth was found (US EPA 2007). It is not reported whether confounders were taken into account.

Summary: No effect of metallic mercury vapour on the fertility of male workers (Lauwerys et al. 1985), no causal relationship with the abortion rate of their wives (Cordier et al. 1991) or with the concentrations of prolactin, testosterone, luteinizing hormone or follicle stimulating hormone in the blood of male workers or of dentists was demonstrated (Erfurth et al. 1990). Female workers in a mercury-vapour lamp factory experienced an increase in menstrual disorders and their primary fertility was reduced (De Rosis et al. 1985). Studies with female dentists or

dental assistants showed an increase in menstrual disorders (Sikorsky et al. 1987). Mercury chloride was correlated with spontaneous abortions, but no details were given in the investigations (Health Council Netherlands 2000). In the available studies, a description of exposure concentrations and internal exposure during the studies is lacking. Furthermore, no confounders were taken into account and/or data on the study evaluation are lacking. As a result, although the data are indicative of an association between exposure to inorganic mercury and an effect on male or female fertility in humans, a quantification of this indication is not possible on the basis of the available studies.

Developmental toxicity

In 153 married female workers at a mercury vapour lamp production plant, in whom exposure to **mercury vapour** at the time of the study had been reduced from above 50 µg/m^3 to below 10 µg/m^3, no increased number of miscarriages was found compared with 193 controls; however, the number of hip joint dislocations in their newborn was increased. The authors point out that the spontaneous frequency of this anomaly varies in different parts of Italy (De Rosis et al. 1985). As no internal exposures were measured in this study, its usefulness for this evaluation is limited.

In a retrospective cohort study (job exposure matrix based on old measurements and personal reports), the effects of **mercury** in workers (136 men, 10 women) at a chloralkali plant were investigated between 1955 and 1994. In the 146 exposed persons 17.1% miscarriages occurred compared to 9.2% in the 119 non-exposed workers. The odds ratio was 2.03 and the P value 0.063 (Frumkin et al. 2001). As no internal exposures were measured in this study, its usefulness for this evaluation is limited.

In 46 female workers exposed to **mercury vapour** (for example in the production of thermometers) (control group of 19 non-exposed women at the same factory) 104 pregnancies occurred between 1948 and 1977. Three offspring of the mothers exposed to 0.025 to 0.23 mg Hg/m^3 had anomalies such as club foot, extrophy of the bladder and anormal anal opening, *spina bifid*a and a mongoloid face. The number of stillborn or abortions was not different to that in the control group (Elghany et al. 1997). Confounders such as diet, smoking or the number of amalgam fillings were not taken into account, and the internal exposure was not determined. This study can therefore not be used for this evaluation.

The effect of **metallic mercury** on reproduction in female dentists and dental assistants (81 women, age 21 to 56) was compared with that in a control group (34 women, age 20 to 46). In the exposed women, the mercury concentration was on average 0.527 mg/kg (controls 0.1 mg/kg) in the scalp hair and 0.381 mg/kg (controls 0.06 mg/kg) in the pubic hair. The Mann-Whitney-U test established an association between the concentration of mercury in the hair and the cases of abortions and malformations. Five children had *spina bifida* (Health Council

Netherlands 2000; Sikorski et al. 1987). The validity of this study has been cast into doubt by other authors as the population, from which the exposed and non-exposed female participants originated, had not been defined. In addition, the control group was not matched for age and medical history. Exposure was determined by the amount of mercury in pubic and scalp hair between 1985 and 1986, but not during pregnancies. The children with *spina bifida* were born in 1972, 1977, 1980, 1982 and 1986. In the opinion of other authors and the Health Council Netherland (2000) the study contains an erroneous interpretation of results and distortion of conclusions.

In female dentists, dental assistants and dental technicians, occupational exposure to **metallic mercury** had no adverse effects on the spontaneous abortion rate, weight at birth, congenital malformations or survival of the 8157 children (Ericson and Källén 1989). Data on exposure concentrations or internal exposure are lacking.

In 349 women exposed to **metallic mercury vapour** at the workplace, the number of complications of parturition (cases of toxicosis, abortions, prolonged parturition, and haemorrhagic parturition) were increased compared with 215 non-exposed controls. This study was inadequately reported, and some of the data on the methods are lacking (WHO 2003).

In another study designed as a follow-up-study in female dental assistants from 12 occupations potentially exposed to **mercury vapour** revealed no increase in abortions in a historical prospective study (Heidam 1984). In addition, no relationship between the amalgam fillings prepared per week and the number of spontaneous abortions or congenital malformations was found in female dental assistants polled in a questionnaire sent by post (WHO 2003).

The effects of long-term exposure to **metallic mercury** were investigated in 241 male workers at an energy plant compared with 254 control persons. No effects on the number of pregnancies of their female partners, children born alive and congenital abnormalities were found (Health Council Netherlands 2000).

In a retrospective cohort study with male workers at a plant belonging to the US Department of Energy in Michigan, USA, long-term exposure to **metallic mercury** (at least 4 months) had no effect on the number of children born alive, congenital abnormalities or illnesses. Urinary mercury concentrations ranged from 2144 to 8572 µg/L. Before actual exposure started, the number of miscarriages was already higher in the "exposed" group (WHO 2003; Health Council Netherlands 2000) (Alcser et al. 1989). An evaluation of a dose-response relationship was not possible on the basis of these data.

A case report describes a three-month-old male infant with dysfunction of the renal tubules, which was attributed to the use of soap containing **mercury iodide** by the mother during pregnancy and the 1-month lactation period. The mother had been using this soap for 15 years to brighten her skin; the infant had never come into contact with it. The concentrations of mercury in the infant's blood and urine were 1.9 µg/100 ml blood and 274 µg/g creatinine, and 9.11 µg/100 ml blood and 784 µg/g creatinine in the mother. When he had reached the age of 8.5 months,

the boy was still found to have 24 µg mercury/g creatinine, slight renal changes and an iron deficiency, but no neurological changes (Lauwerys et al. 1987). The effects occurring in this case report cannot be used to assess mercury in the context of hazard to offspring during pregnancy, as no difference can be drawn between prenatal and postnatal exposure, and because mercury is also eliminated via the mother's milk (Health Council Netherlands 2000).

Summary: Some studies revealed increased incidences of abortions (Frumkin et al. 2001; Sikorski et al. 1987) and malformations in children (De Rosis et al. 1985; Elghany et al. 1997; Sikorski et al. 1987) whose mothers had been exposed to metallic mercury during pregnancy in factories or dental practices. In other studies, no increased incidences of abortion occurred (De Rosis et al. 1985; Elghany et al. 1997; Ericson and Källén 1989; Heidam 1984) and no increased number of malformations were found (Ericson and Källén 1989). All studies can only be used to a limited extent for the assessment of the developmental toxicity of mercury and inorganic mercury compounds, as for the most part no exposures during pregnancy were recorded, and data on methodology or on evaluation of the studies are lacking.

Postnatal toxicity

Mercury is eliminated with the mother's milk (Health Council Netherlands 2000). In an infant aged three months, tubular dysfunction of the renal tubules was found after the mother had used soap containing **mercury iodide** during pregnancy and the 1-month lactation period (see above; Lauwerys et al. 1987). The effects occurring in this case report cannot be used for the assessment of hazards of mercury to the offspring during pregnancy, as no difference can be made between prenatal and postnatal exposure, and because mercury is eliminated with the mother's milk.

4.6 Genotoxicity

As already described in the 1999 documentation (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German), studies on the genotoxicity of **elemental mercury** in exposed workers yielded both negative and positive results (acentric fragments, aneuploidies, sister chromatid exchanges, micronuclei). However, their relevance is greatly limited due to methodological shortcomings, inadequate accounting of possible confounders or due to the absence of a dose-response relationship between urinary mercury concentrations and observed effects. Studies in workers with exposure to **mercury(II) chloride** and organic mercury compounds or **mercury fulminate [$Hg(CNO)_2$]** showed an increased number of chromosome aberrations in the lymphocytes. Both studies are only usable with limitations (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

In more recent investigations in 68 persons, of whom 44 had received tooth fillings with amalgam (consisting of 50% mercury, 35% silver, 15% tin as well as copper, zinc and possibly cadmium) or composites or both, the peripheral blood lymphocytes were investigated for DNA damage in the comet assay under alkaline conditions. Exposure to amalgam alone was only present in 10 persons. DNA migration increased in total with the number of fillings, and was significantly increased compared with controls. An association between DNA damage and age (3 categories: 18–19; 20–22; >23 years) was found in the exposed group, but not in the control group consisting of patients without fillings (Di Pietro et al. 2008). The exposure is insufficiently characterized, as the parameter "number of amalgam fillings" is not adequate to describe it. Biomonitoring investigations of blood or urine to determine the actual exposure to mercury are not available. Also, the number of work processes involving amalgam fillings during or before the study or confounders such as fish consumption is not given. For this reason, the study cannot be taken as confirmation for genotoxic effects of mercury.

In 25 workers (average age 37.8 years) exposed to **mercury** for 2 to 35 years and in 50 controls (average age 38.5 years), peripheral blood lymphocytes were examined in an alkaline comet assay, in a sister chromatid exchange test and in a test for chromosome aberrations. The mean concentration of mercury in the air at the workplace was 0.025 mg/m^3 for the exposed workers. The mean mercury concentrations were 109 µg/L in urine and 19 µg/L in blood. Compared with controls, no changes in "tail moment" in the comet assay and no increased sister chromatid exchanges were found. However, chromosome aberrations were significantly increased, and an increased "tail length" was observed in the comet assay. After exposure of the lymphocytes to radiation (2 Gy), the test for DNA repair capacity in the subsequent comet assay immediately after radiation yielded no significant differences between the investigated groups with regard to tail moment and tail length. After two hours, significantly higher values were observed in the exposed persons for tail moment and tail length in the comet assay. The irradiated lymphocytes of the exposed workers showed significantly lower DNA repair capacities than controls. After subjecting the lymphocytes to radiation with UV-C 6J/m^2 there were no group differences in the comet assay including the repair capacity (Cebulska-Wasilewska et al. 2005). In this study, the mercury concentrations in the exposed workers were within the range of biological threshold values and clearly above those of the not occupationally exposed general population (0.89 µg/L in urine and 0.86 µg/L in blood; arithmetic mean; Umweltbundesamt 2002). This study's relevance is limited for methodological reasons, as important data on the recruitment of the exposed industry workers (for example response rate) and selection of non-exposed persons (students, teachers, office employees, accountants or farm worker from the area surrounding Cracow) are lacking. A relevant selection bias is possible both in the exposed as well as in the non-exposed groups. In addition, the study is described by the authors as being a case-control study, despite the fact that it compares both exposed and non-exposed persons but not, however, cases and controls.

Summary: Even including the most recent studies, the genotoxic potential of ele-

mental mercury or inorganic mercury compounds in humans cannot be evaluated conclusively.

4.7 Carcinogenicity

In the documentation of 1999 (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German), it was stated that the case-control studies and studies on cancer incidence or mortality available at the time, which were for the most part carried out with relatively low exposed collectives in choralkali electrolysis plants, in the dental medical field, as well as in the production of nuclear weapons, no clear indications of a carcinogenic effects of mercury vapours were found. Collectives with previous, far higher exposures (for example mine workers) were not sufficiently investigated in the context of this endpoint. Therefore, the data for a conclusive assessment were insufficient (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German). More recent studies available on this subject are not available.

5 Animal experiments and in vitro studies

5.1 Acute toxicity

5.1.1 Inhalation

Exposure to **mercury vapour** at a concentration of 29 mg/m^3 for two hours was lethal for 20 of 32 rats. A concentration of 27 mg/m^3 for 20 hours was survived by rabbits. One of two animals exposed for 30 hours died. The cause of death was acute lung failure (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

Wild type and knockout mice without metallothionein were exposed once to **mercury vapour** at concentrations of 5.5 to 6.5 mg/m^3 for three hours, and their lungs examined 12 and 24 hours afterwards. Atelectasis, blood coagulations and haemorrhages were found in the lungs of the exposed animals, though there were no differences between the knockout and the wild type mice. An increased accumulation of mercury in the alveolar macrophages and sometimes also in the alveolar epithelium was found in the exposed animals. As changes in the basal membranes, dissociations and a reduced density of the matrix were observed (Shimada et al. 2004).

5.1.2 Ingestion

The LD_{50} of **mercury(II) chloride** for the rat is in the range between 26 and 78 mg/kg body weight calculated as mercury (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

5.2 Subacute, subchronic and chronic toxicity

In the documentations for the MAK value of 1999 (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German) and the BAT value of 2005 (see Supplement "Mercury and its anorganic compounds", 2006, only available in German), it is stated that the most sensitive endpoints after repeated intake of mercury and its inorganic compounds are kidney toxicity and neurotoxicity. Because the data from animal studies play only a subordinate role in the establishment of a workplace threshold concentration for mercury, they have not been described in detail here. The reader is referred to other reviews.

5.2.1 Inhalation

In the few available animal studies of the toxicity caused by repeated exposure to **mercury vapour**, the target organs proved to be the same as in humans, the nervous system and the kidneys. The concentrations tested were mostly very high (at least 0.8 mg/m^3) so that other organ systems were also affected and a concentration without effect was not found. According to one study carried out in the 1950s, exposure of rats, rabbits and dogs to a mercury concentration of 0.1 mg/m^3 (7 hours daily, 5 days per week for up to 83 weeks) did not result in histological changes in brain, kidneys, liver or lungs. Kidney function parameters and neurological parameters were not recorded (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German)

OLA129/C57BL6 wild type mice and knockout mice without metallothionein were exposed to **mercury vapour** at a concentration of 0.06 mg/m^3 on 8 hours per day for 23 weeks and examined for neurobehavioral effects after 12 and 23 weeks (open-field, passive avoidance test). At a concentration of less than 1 ppm Hg in the brain (mg/kg mercury in tissue), the exposed animals showed an increased locomotion in the open-field test and poorer performance in the avoidance test; the performance of the knockout-animals was somewhat poorer than that of the wild type animals (Yoshida et al. 2004).

5.2.2 Ingestion

In experimental animals which had ingested **mercury(II) chloride,** the most sensitive target organ was the kidney. Oral administration of the substance on

5 days weekly for 6 months to F344 rats resulted in increases in relative and absolute kidney weights in males from the lowest tested dose of 0.31 mg/kg body weight and in females from 0.63 mg/kg body weight. The histological examination revealed an increase in the severity of nephropathy. The kidney damage increased in severity with the dose. In female mice the no observed effect level (NOEL) was 5 mg/kg body weight, in male mice 2.5 mg/kg body weight. In numerous other studies with various species, the doses administered were much higher and all in the active range so that no NOELs can be derived (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

No recent studies relevant for assessment are available.

5.3 Local effects on skin and mucous membranes

There are still no data available.

5.4 Allergenic effects

In various animal experiments Sensitization caused by inorganic mercury compounds has been demonstrated (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

Skin sensitization

Ten Brown Norway rats with a genetic predisposition to form an increased T cell reactivity following exposure to elemental mercury and ten Lewis rats without this predisposition were sensitized by five subcutaneous **mercury(II) chloride** injections of 1 mg/kg body weight in isotonic saline solution administered at 2-day intervals respectively. Amalgam plates or plates from a mercury-free alloy were attached for 20 days to the oral mucosa in two groups consisting of 5 sensitized animals of both strains and two groups of 5 non-pretreated control animals each of both strains. Lichenoid changes in mucosa were found equally in the animals pretreated with **mercury(II) chloride** and those not pretreated, independently of the type of alloy used. In the patch test with 5% **amalgam** and 1% **mercuric amidochloride** in petrolatum as well as 0.1% **thiomersal**, more positive reactions to the mercury compounds (positive reaction to 20 of 80 application sites) were found in the animals pretreated with **mercury(II) chloride** than in the non-pretreated animals (positive reaction to 8 of 95 application sites). Two animals per group reacted to mercury(II) chloride and the mercury-free alloy in the pretreated group, but not in the non-pretreated group. The findings showed no correlation between

positive test result and animal strain, the type of alloy used, or the extent to which lichenoid mucous membrane changes were formed (Dunsche et al. 2003 a).

Respiratory tract

There are still no findings available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Results from fertility studies are shown in Table 1.

Mercury affects female reproduction at different sites along the hypothalamic-pituitary-ovarian axis. For example, mercury chloride, but not methyl mercury produced an inhibition of ovulation. Mercury accumulates in the *corpora lutea*, the sinusoids of the pituitary and in the arcuate nucleus of the hypothalamus in female hamsters; the FSH (follicle-stimulating hormone) level in the pituitary of treated animals also increases (Tan et al. 2009).

Male knockout mice, in which the oestrogen receptor α was absent, were infertile. Fertility was retained when oestrogen receptor β was absent (Tan et al. 2009). Mercury shows spermatotoxic effects, its concentration in the seminal fluid correlates with the extent of damage (Tan et al. 2009).

Generation studies

Mercury(II) chloride was administered by gavage to groups of 25 male and female C57BL/6 mice at 0, 0.25, 0.5 or 1 mg **mercury(II) chloride**/kg body weight and day. In a 14-day range-finding study, 1 mg/kg body weight and day was the maximum tolerated mercury chloride dose in this strain of mice. The males were treated 40 days before mating and during the 21-day mating period and, immediately afterwards, subjected to histopathological examination. The females were treated from day 16 prior to mating up to the end of the 21-day lactation period. The number of pregnant animals was only 4/25 (16%) in all exposure groups, and was thus significantly lower than in the control group with 11/25 (44%); this was markedly lower than in the laboratory controls with 85%. However, this pregnancy rate relates to C57Bl/6 mice of a different origin and to a different study protocol (continuous breeding). The number of implantations, the body weight of the dams after parturition, clinical pathology of parent animals and body weight gain in the parents of both sexes showed no significant difference between dosed groups and the controls. In the dams, the relative kidney weight was significantly decreased at 0.5 and 1 mg/kg body weight and day. Mercury accumulation was dose-dependent

Table 1 Studies on fertility after exposure to mercury vapour or administration of inorganic mercury compounds

Species, strain, number per group	Exposure	Findings	References
Generation studies			
mouse, C57BL/6, 25 ♂/ 25 ♀ per group	**40 days (♂) or 16 days (♀) before mating up to LD 21** 0, 0.25, 0.5, 1 mg **$HgCl_2$**/kg body weight and day (0, 0.19, 0.37, 0.74 mg Hg^{2+}/kg body weight and day), gavage	**at 0.19 mg Hg^{2+}/kg body weight and above**: number of pregnant animals reduced (no dose-dependency; fertility of control animals very low), **study of limited validity**	Kahn et al. 2004
Female fertility			
rat, no other details, ♀	**21 days**, 0, 2.5 mg **Hg**/m^3, 6 hours/day	**0 mg Hg/m^3**: prolonged oestrous cycle (4.5 to 5.1 days) **2.5 mg Hg/m^3**: prolonged oestrous cycle (4.3 to 6.7 days)	Health Council Netherlands 2000; Kahn et al. 2004
rat, no other details, ♀ 18 exposed, 23 controls	**6–8 weeks**, 0, 2.5 mg **Hg**/m^3, 6 hours/day	**2.5 mg Hg/m^3**: mean body weight decreased (not significantly)	Health Council Netherlands 2000; Kahn et al. 2004
rat, Sprague Dawley, 42/ 9/15/18 ♀	**11 days**, 0, 1, 2, 4 mg **Hg**/m^3, 2 hours/day, nose-only exposure	**at 2 mg Hg/m^3** and above change in oestrous cycle **4 mg Hg/m^3**: body weight decreased, no effect on absolute and relative organ weight (brain, kidneys, liver, uterus), serum oestradiol concentration decreased and serum progesterone concentration increased	Davis et al. 2001
6–12 ♀ per group	**8 days**, 2 mg **Hg**/m^3; 2 hours/day, exposure start in metoestrus, nose-only exposure	**2 mg Hg/m^3**: relative liver weight decreased (relevance questionable), *corpora lutea* of exposed rats appeared immature, no effect on number of *corpora lutea* or ovulation, oestrous cycle prolonged, no significant effects on oestrogen/progesterone ratio	

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
4–7 ♀ per group	**8 days**, 0, 2 mg **Hg**/m^3; 2 hours/day, exposure start 5 days before or after mating, nose-only exposure	**2 mg Hg/m^3**: no effect on the number of implantations and *corpora lutea*, no significant effects on oestrogen/progesterone ratio	
mouse, Kud:ddY, 10♀ per group	**single GD 0**, 0, 0.5, 1.0, 1.5, 2.0, 2.5 mg Hg^{2+}/kg body weight (as **$HgCl_2$**), intravenous	**at 1.5 mg Hg^{2+}/kg body weight and above**: number of abnormal embryos (GD 3.5) increased	Kajiwara and Inouye 1986
hamster, golden hamster, ♀	**4–8 days**, 0, 0.2, 1 mg **$HgCl_2$**/kg body weight and day (0.15, 0.74 mg Hg^{2+}/kg body weight and day), subcutaneous	**0.74 mg Hg^{2+}/kg body weight**: delay or inhibition of oestrous cycle, follicle maturation decreased, hypertrophy of the uterus decreased, morphological change, *corpora lutea* prolonged, progesterone in *corpora lutea* decreased	Lamperti and Printz 1973
mouse, 10 ♀ per group	**8 days**, 0, 0.1 mg **$Hg(NO_3)_2$**/kg body weight and day (4 mg Hg^{2+}/kg body weight and day), subcutaneous	**4 mg Hg^{2+}/kg body weight**: number of oestrous cycles decreased, duration of dioestrus increased	Health Council Netherlands 2000
	12 days, 0, 0.2 mg **$Hg(NO_3)_2$**/kg body weight and day (8 mg Hg^{2+}/kg body weight and day), subcutaneous	**8 mg Hg^{2+}/kg body weight**: no or one oestrous cycle, duration of dioestrus increased	
mouse, (101×C3H) F1, ♀	**single**, 0, 1.48 mg Hg^{2+}/kg body weight (as **$HgCl_2$**), intraperitoneal	**1.48 mg Hg^{2+}/kg body weight**: number of implantations increased, number of live foetuses decreased, number of litters and offspring per female decreased	Suter 1975

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
mouse, (SEC× C57BL) F1 and (SEC× C57BL) F1×XGSY, ♀	**single**, 0, 1.48 mg Hg^{2+}/kg body weight (as **$HgCl_2$**), intraperitoneal	**1.48 mg Hg^{2+}/kg body weight**: no effects	Suter 1975
Male fertility			
rat, Albino, 20♂ per group	**90 days**, 0, 0.05, 0.1 mg **$HgCl_2$**/kg body weight and day (0.037, 0.074 mg Hg^{2+}/kg body weight and day), intraperitoneal	**at 0.037 mg Hg^{2+}/kg body weight and above**: body weight gain decreased, activity of 3β-hydroxy-δ-5-steroid dehydrogenase decreased	Chowdhury et al. 1985
rat, Wistar, 18 ♂ exposed, 12 ♂ controls	**single**, 0, 1 mg **$HgCl_2$**/kg body weight (0.74 mg Hg^{2+}/kg body weight), intraperitoneal	**0.74 mg Hg^{2+}/kg body weight**: degenerated seminiferous tubules 1, 3, 5, 8 and 12 days after treatment	Prem et al. 1992
mouse, CDF1, 10 ♂ per group	**single**, 0, 1 mg Hg^{2+}/kg body weight (as **$HgCl_2$**), intraperitoneal	**1 mg Hg^{2+}/kg body weight**: fertility decreased 21–56 days after injection, incorporation of thymidine, uridine and L-leucine in sperm cells inhibited, effect mostly on spermatogonia, premeiotic spermatocytes and early elongated spermatids (no effect on spermatozoa in testis, epididymis and vas deferens)	Lee and Dixon 1975
mouse, rat, hamster, guinea pig, ♂	**4 weeks**, 0, 1, 2, 5 mg **$HgCl_2$**/kg body weight and day (0, 0.74, 1.48, 3.7 mg Hg^{2+}/kg body weight and day), intraperitoneal	**0.74 mg Hg^{2+}/kg body weight**: Hamster: testicular degeneration, rat/mouse: partial testicular degeneration **1.48 mg Hg^{2+}/kg body weight**: all species: inhibition of spermatogenesis, atrophy of Leydig cells **3.7 mg Hg^{2+}/kg body weight**: all species: testes weight decreased, degeneration and deformation of Leydig cells and seminiferous tubules	Chowdhury and Arora 1982

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
mouse, Swiss, 7 ♂ per group	**1, 2, 3 weeks**, 0, 0.5 ppm **$HgCl_2$** in water (0, 0.5 mg/L)	3β- and 17β-hydroxysteroid dehydrogenase activitydecreased, degeneration of connective tissue of testes, changes in seminiferous tubules, changes in primary and secondary spermatocytes, hypertrophy and vacuolization of interstitial and Sertoli cells, testosterone in blood decreased	Nagar und Bhattacharya 2001

in the kidneys of the parents, more in males than in females were no histopathological findings. The average numbers of live pups per litter were obtained from the data as 57/11 (5.18 = controls), 29/4 (7.25), 28/4 (7.0) and 17/4 (4.25) (Kahn et al. 2004). They do not agree with the average numbers of live pups per litter given in the publication as 6.49 (controls); 7.25, 7.50 and 5.68. In addition, the statement that 17 offspring were born alive and 3 stillborn (17/20 = 85%) in the high dose group resulting in a live birth index of 15%, is not reproducible. The validity of this study is thus limited due to the animals' low fertility and the inconsistent results. Considering that a further generation study is absent, the results must however be seen as evidence for effects that cannot be excluded.

Female fertility

Exposure of 24 female rats to **mercury vapour** at concentrations of 0 or 2.5 mg/m^3 on six hours daily for 21 days resulted in a significantly prolonged oestrous cycle in the exposed animals. The mean value increased from 4.3 to 6.7 days. In the control animals, the length of the cycle increased from 4.5 to 5.1 days during the same period. In another investigation, female rats were exposed six hours daily to **metallic mercury vapour** at concentrations of 0 or 2.5 mg/m^3 over six to eight weeks before being mated. All 18 exposed and 23 control animals that were mated were pregnant. The total number of exposed and control animals was not given. The exposed animals had a non-significantly reduced mean body weight (no other details). As regards the mean number of offspring per litter or the number of live offspring per litter, no difference was found between the exposed and the non-exposed animals (Health Council Netherlands 2000; Kahn et al. 2004).

On 11 subsequent days, female rats were exposed 2 hours daily to **mercury vapour** at concentrations of 0, 1, 2 or 4 mg/m^3. The tissue concentrations in kidneys and brain correlated with exposure concentration and exposure duration. A concentration of 4 mg/m^3 was toxic and decreased body weight. The urinary mercury

levels at 2 mg/m3 group were about 2-fold greater than at 1 mg/m3, whereas they were 16-fold greater in the 4 mg/m^3 group than in the 2 mg/m^3 group. Therefore, a saturated uptake at 4 mg/m^3 can be concluded. Increased relative liver weights and increased length of oestrous cycles without toxicity occurred at 2 mg/m^3, toxicity and changed oestradiol and serum progesterone concentrations at 4 mg/m^3. When female animals were exposed to **mercury vapour** at a concentration of 2 mg/m^3 for 8 days, the relative liver weight was decreased and the length of the oestrous cycle increased (Davis et al. 2001).

Female mice received single intravenous injections of mercury in the form of **mercury(II) chloride** at doses of 0, 0.5, 1.0, 1.5, 2.0 or 2.5 mg/kg body weight directly after mating. Three and a half days after mating, the number of abnormal embryos was 19/96 (19.8% = controls), 17/84 (20.2%), 28/90 (31.1%), 63/113 (55.8%), 53/94 (56.4%) and 102/110 (92.7%), and was significantly increased from 1.5 mg/kg body weight. Dams with a low blood mercury concentration of about 0.1 μg/ml had normal embryos, abnormal embryos were observed at blood mercury concentrations above 4 μg/ml. The blood mercury concentrations were at their highest six hours after treatment, half as high after 24 hours, and remained almost constant up to the end of the study (Kajiwara and Inouye 1986).

Female hamsters were given **mercury(II) chloride** subcutaneously at daily doses of 0.2 mg/kg body weight for 8 days, or 1 mg/kg body weight on four subsequent days. The 1 mg/kg dose produced an interruption in the oestrous cycle. Both maturation of follicles was retarded and normal hypertrophy in the uterus was delayed to inhibited. The physiological regression of the *corpora lutea* was delayed and the progesterone levels in the *corpora lutea* were decreased, but not in the interstitium (Lamperti and Printz 1973).

Ten female mice with normal cycles received subcutaneous injections of 0.1 mg **mercury(II) nitrate** per day for 8 days, or 0.2 mg mercury(II) nitrate per day for twelve days (about 4 or 8 mg mercury/kg body weight and day). In the low dose group, 3/10 animals had no oestrous cycle at all, the remaining animals had not more than one during the eight day exposure. The cycles normalized during the twelve days after the end of treatment. At 0.2 mg per day, no cycle occurred in 4/10 animals and only one in 3/10 animals. The duration of dioestrus increased from 30% of the cycle length before treatment to 70% during treatment. In the 15-day recovery period, 4/10 animals had no oestrous period and only one of these animals an anoestrus during the treatment period. The percentage of days in the dioestrus was 45% during the recovery period lasting 15 days. No data on general toxicity were reported, although the dosages were in a range at which toxic effects were found in other studies (Health Council Netherlands 2000).

Administration of a single intraperitoneal dose of **mercury(II) chloride** at 2 mg/kg body weight (mercury equivalent 1.48 mg/kg body weight) to female (101×C3H) F1 mice resulted in a reduced number of implantations and live foetuses and a significant increase in dead implantations. Three strains of mice were compared. A reduced number of litters and offspring per female occurred within one year in the

(101×C3H)F1 strain. This was not observed in the (SEC×C57BL)F1 and (SEC×C57BL) F1×$X^{GS}Y$ strains after analogous treatment (Suter 1975).

Male fertility

Rats received intraperitoneal injections of **mercury(II) chloride** at doses of 0.05 or 0.1 mg/kg body weight and day for 90 days. 3β-Hydroxy-δ-5-steroid dehydrogenase, which activates the last step in testosterone synthesis, was dose-dependently inhibited in the testicular tissue (Chowdhury et al. 1985).

After single intraperitoneal injection of a mercury dose of 0.74 mg/kg body weight in the form of **mercury(II) chloride**, the seminiferous tubules of male rats were degenerated. In particular, the tubules in stages IX to XII were affected (Prem et al. 1992).

Effects on spermatogenesis, fertility and testis histology were studied in mice after a single intraperitoneal dose of **mercury(II) chloride** equivalent to 1 mg mercury per kg body weight. To record the effects on fertility, the animals were mated with a new female every week for 70 days. Each of these females was investigated nine days after termination of mating. Compared with the controls, male fertility was significantly reduced from day 21 to 56 after administration of the substance, the lowest fertility level being found at 50% after 35 days. No histopathological changes in the testes were found. The transient reduction in fertility could be related to an effect on spermatogonia and premeiotic spermatocytes which was less than that obtained with methyl mercury at the same dose (Lee and Dixon 1975). No data on general toxicity were reported; however, the doses were in a range at which toxic effects were found in other studies.

Testicular changes were investigated in rats, mice, guinea pigs and hamsters after intraperitoneal injections of **mercury(II) chloride** in doses of 1, 2 or 5 mg/kg body weight and day for 4 weeks. Five mg/kg body weight and day produced degeneration and cellular deformations in the Leydig cells and seminiferous tubules in all species, the testes weights were significantly reduced. At 2 mg/kg body weight and day, no cellular deformations occurred, though an inhibition of spermatogenesis and Leydig cell atrophy were observed. At 1 mg/kg body weight and day, degeneration occurred in the testes of hamsters, only partial degeneration was observed in rats and mice. The guinea pigs were without unusual findings. Nothing was reported concerning general toxicity. The LD_{50} was in the range of 14 to 25 mg/kg body weight in these species (Chowdhury and Arora 1982).

Seven male Swiss mice per group were treated (no details on application method) for 7, 14 or 21 days with 0.5 ml of an aqueous solution (0.5 mg/L) containing 0 or 0.5 ppm **mercury(II) chloride**. The activity of 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase in the testis was dose- and time-dependently reduced. In addition, the serum testosterone concentration was reduced in the exposed animals. At all times during the investigation, degeneration of the testicular connective tissue, changes in the seminiferous tubules, in the primary and

secondary spermatocytes, and hypertrophy and vacuolization of interstitial and Sertoli cells were found. The effects were still not significant after seven days (Nagar and Bhattacharya 2001). A clear dose-dependency and time-dependency was found only for the reduced activity of 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase in the testis.

Summary: Generation studies: No valid generation studies are available. On the basis of an oral one-generation study in the mouse of limited validity (Kahn et al. 2004) impairment of fertility cannot be excluded for **mercury(II) chloride** even at the lowest dose of 0.25 mg/kg body weight and day (0.19 mg Hg^{2+}/kg body weight and day).

Female fertility: Exposure of female rats to **mercury vapour** caused a significant prolongation of the oestrous cycle at 2 mg/m^3 and above (Davis et al. 2001). Subcutaneous injection of **mercury(II) nitrate** (about 4 or 8 mg Hg^{2+}/kg body weight and day) for 8 or 12 days prolonged the cycle duration of female mice up to and including anoestrous (Health Council Netherlands 2000). Also in hamsters, the oestrous cycle was inhibited by subcutaneous injections of **mercury(II) chloride** (0.74 mg Hg^{2+}/kg body weight) (Lamperti and Printz 1973). A disturbance of implantation and thus a reduced litter size occurred in mice after single intravenous or intraperitoneal injection of about 1.5 mg Hg^{2+}/kg body weight (Kajiwara and Inouye 1986; Suter 1975).

Male fertility: Single intraperitoneal administration of **mercury(II) chloride** (about 1 mg Hg^{2+}/kg body weight) to male mice resulted in reduced fertility through effects on spermatogonia and premeiotic spermatocytes (Lee and Dixon 1975). In rats, degenerated seminiferous tubules were already observed after single intraperitoneal injection of a mercury dose of 0.74 mg/kg body weight (administered as $HgCl_2$) (Prem et al. 1992). After repeated intraperitoneal injection, also at higher doses, an inhibition of spermatogenesis (at 1.48 mg Hg^{2+}/kg body weight and day and above) and degeneration and cellular deformations in the Leydig cells and seminiferous tubules occurred in rats, mice, hamsters and guinea pigs (Chowdhury and Arora 1982; Prem et al. 1992). Changes in sex hormone concentrations were also reported in male mice after oral administration of mercury chloride (Nagar and Bhattacharya 2001).

Conclusion: Mercury vapour and inorganic mercury compounds have effects on fertility. It is not possible to derive either a NOAEC or a NOAEL. From a one-generation study in mice (Kahn et al. 2004) of limited validity, an impaired fertility at 0.19 mg Hg^{2+}/kg body weight and day cannot be excluded. Effects on the oestrous cycle were observed at 2 mg Hg/m^3 in female rats and after subcutaneous administration of 0.74 mg Hg^{2+}/kg body weight and day in female hamsters, and effects on spermatogenesis in male rats after subcutaneous injection of 0.74 mg Hg^{2+}/kg body weight.

5.5.2 Developmental toxicity

Studies with mercury vapour

Table 2 shows the results from developmental toxicity studies with exposure to mercury vapour.

Table 2 Results from developmental toxicity studies with exposure to mercury vapour

Species, strain, number per group	Exposure	Findings	References
Prenatal exposure and investigation			
rat, Long Evans, 25 ♀ per group	**GD 6–15**, 0, 1, 2, 4, 8 mg Hg/m³, nose-only, 2 hours/day; investigation on GD 6, 10, 15 or PND 1 (5 animals/ group)	**at 1 mg Hg/m³: and above** dams: protein in urine increased, ALP in urine increased **2 mg/m³**: dams: NOAEC **at 4 mg Hg/m³ and above**: dams: DD body weight gain decreased, kidney weight increased (no histopathological finding) offspring: NOAEC **8 mg Hg/m³:** dams: tremor, unsteady gait, body weight decrease 13%, moribund killed on PND 1 offspring: number of absorptions increased (GD 15), litter size decreased, body weight decreased on PND 1	Morgan et al. 2002
rat, no other details, 8 ♀ per group	**3 weeks before mating and GD 7–20**, 0, 2.5 mg Hg/m³, 6 hours/day; investigation on GD 20	**2.5 mg Hg/m³**: foetuses: number of live foetuses decreased dams: no details	Health Council Netherlands 2000
Prenatal exposure and postnatal investigation			
rat, Sprague Dawley, 8 ♀ per group	**GD 6–11**, 0, 1.5 mg Hg/m³ for 1, 3 hours/day; investigation on PND 3, 6, 21, 60	Investigation of cholinergicic neurons in the brain **1.5 mg Hg/m³ 1** h: PND 6: mRNA of p75 NGF in medial septal nucleus and diagonal band of the broca decreased, PND21: NGF receptors in basal forebrain 40% decreased	Söderström et al. 1995

Table 2 (Continued)

Species, strain, number per group	Exposure	Findings	References
		1.5 mg Hg/m³ 3 h: PND 6: mRNA of p75 NGF in medial septal nucleus increased PND 21: NGF receptors in hippocampus 62% increased, in basal forebrain 50% decreased, mRNA of p75 NGF in medial septal nucleus and diagonal band of the broca decreased, PND 60: no significant changes in cortex, hippocampus, septum, cerebellum	
	GD 13–18, 0, 1.5 mg Hg/m³ for 1, 3 hours/day; investigation on PND 21, 60	**1.5 mg Hg/m³ 1 h:** PND 60: NGF receptors in hippocampus increased **1.5 mg Hg/m³ 3 h:** PND 21: NGF receptors in cortex increased, PND 60: NGF receptors in cortex and hippocampus increased	
rat, Sprague Dawley, 12♀	**GD 14–19**, 0, 1.8 mg Hg/m³, 1.5 hours/day (about 0.1 mg Hg/kg body weight and day); investigation: up to 5 months *post partum*	**1.8 mg Hg/m³: 1.5 hours/day**: 4 months: spontaneous motor activity increased; 4.5 months: learning time in swim maze increased; 5 months: learning time in radial arm maze increased	Fredriksson et al. 1996
rat, Sprague Dawley, 12 ♀ per group	**GD 11–14 + 17–20,** 1.8 mg Hg/m³, 1 hours/day or 3 hours/day (about 0.2 or 0.07 mg Hg/kg body weight and day); investigation: 3, 4, 7, 14, 15 months *post partum*	**1.8 mg Hg/m³ 1 and 3 hours/day**: 3 months: locomotion decreased, number and duration of rearing decreased, total activitydecreased; 4 months: learning time radial arm maze increased, 7 and 14 and 15 months: no significant differences between exposed and non-exposed animals	Danielsson et al. 1993
rat, Long Evans, 12 ♀ per group	**GD 6–15,** 0, 4 mg Hg/m³, nose-only, 2 hours/day; investigation: 180 days *post partum*	**4 mg Hg/m³ 2 hours/day**: about 6 months: no changes in nerve function or nerve conduction velocity	Herr et al. 2004

Table 2 (Continued)

Species, strain, number per group	Exposure	Findings	References
rat, no other details, 12 ♀ per group	**3 weeks before mating and GD 7–20**, 0, 2.5 mg Hg/m³, 6 hours/day; investigation: to to 8 weeks *post partum*	**2.5 mg Hg/m³:** dams: body weight gain not significant decreased; pups: number of live births decreased, 96% mortality to PND 4, 100% mortality to weaning, ♀: after 8 weeks kidney and liver weight decreased, ovarian weight increased	Health Council Netherlands 2000
squirrel monkey, 10 ♀ per group	**from 3rd/7th to 22nd pregnancy week**, 0, 1 mg Hg/m³, 24 hours/day (n = 1), 7 hours/day (n = 4) or 4 hours/day (n = 5); 5 days/week; investigation: no details	**1 mg Hg/m³:** dams: number of abortions increased, abnormal pregnancies increased, no signs of toxicity offspring: body weight decreased, mortality increased, brain weight decreased, cerebral sulci irregular, sulci immature, disoriented pyramidal neurons in cortex, number of heterotopic neurons in brain with disoriented dendrites increased	Berlin et al. 1992
squirrel monkey, 6 ♀ per group	**from 3rd/7th to 22nd pregnancy week**, 0, 0.5, 1 mg Hg/m³, 7 hours/day (n = 1) or 4 hours/day (n = 2); 5 days/week; investigation: no details	**at 0.5 mg Hg/m³:amd above** offspring (0.8–4 years old): performance in lever pressing decreased **up to 1 mg Hg/m³**: offspring: no effects on weights at birth or body weight gain	Newland et al. 1996
Postnatal exposure and investigation			
rat, Sprague Dawley, 10 ♀ per group	**PND 11–17**, 0, 0.05 mg Hg/m³, 1 hour/day or 4 hours/day; investigation: 2 and 4 months *post partum*	**0.05 mg Hg/m³:** hyperactivity, retarded spatial learning capacity (especially marked when exposed 4 hours/day)	Fredriksson et al. 1992

ALP: alkaline phosphatase, DD: dose-dependent, GD: gestation day, NGF: nerve growth factor, PND: postnatal day

Prenatal exposure and investigation

Long Evans rats were exposed to **mercury vapour** at concentrations of 0, 1, 2, 4 or 8 mg/m^3 for two hours per day from days 6 to 15 of gestation. Five dams per group and their foetuses or newborns were investigated on gestation days 6, 10 or 15 and on the 1st day after birth, and a number of dams also on day 21 after birth. The amount of mercury in maternal tissue increased with exposure concentration and duration, and was highest in the kidneys. In the week between the end of exposure and the investigation, about 70% of the mercury was eliminated from the maternal tissue; elimination from brain and kidneys was slowest. One possible reason could be the high concentration of metallothionein in these tissues. The concentration of mercury in foetal tissues increased with exposure concentration and duration. One week after the end of exposure, significant amounts of mercury in the brain, liver and kidneys could still be found in the neonates on the first day after birth. The total amount of mercury in the neonatal brain continued to increase after termination of inhalation exposure, suggesting a redistribution of mercury from the dam to neonatal brain. Metallothionein levels in neonatal tissues, which were determined only in the 4 mg/m^3 concentration group, were not increased. Up to 4 mg/m^3, there were no effects on the number of resorptions, postnatal litter size or neonatal body weight. At 8 mg/m^3, the number of resorptions was increased on gestation day 15, litter size and weight at birth of the offspring were decreased. Maternal toxicity was observed at this dose level. On postnatal day one the organ weights of the offspring were not significantly different from controls, the amount of mercury in the brain, kidneys and liver was however still 5 to 20 times higher than in the controls (Morgan et al. 2002). The maternal NOAEC in this investigation was 2 mg/m^3, that for the offspring was 4 mg/m^3, at which level first signs of maternal toxicity occurred. No skeletal and visceral investigations of the foetuses were carried out in this study.

Female rats were exposed to metallic **mercury vapour** three weeks before mating and from gestation days 7 to 20 at 0 or 2.5 mg/m^3 six hours per day. After caesarian section, the number of live foetuses was reduced. This was attributed to a decreased number of implantations reflecting a decrease in ovulation or increased preimplantation loss (Health Council Netherlands 2000). It is not reported whether histological investigations of the foetuses or pups were performed. As only one concentration was tested, no NOAEC is obtained from this study.

Prenatal exposure and postnatal investigation

In an exposure chamber, pregnant rats were exposed from gestation days 6 to 11 or 13 to 18 one hour or three hours daily to **mercury vapour** at concentrations of 0 or 1.5 mg/m^3. On day 21 or 60 after birth, different regions of the brain in the exposed animals were investigated especially for their concentration in nerve growth factors (NGF) p75 and p140, Changes in the expression of mRNA encoding NGF, the low-affinity and high-affinity receptors for NGF and choline acetyltransferase were also determined. In the prenatally exposed animals, sometimes there were marked changes in different regions of the brain. The size of the neurons in the basal forebrain was, however, not changed (Söderström et al. 1995).

Rats were exposed to **mercury vapour** at a concentration of 1.8 mg/m³ for 1.5 hours daily from gestation days 14 to 19, and the offspring investigated for behaviour abnormalities. On day 2 or 3 after birth in 12 pups, one per litter, the concentration of mercury in the brain was 5 ± 2 ng/g tissue in the exposed animals and 1 ± 1 ng/g tissue in the control animals. Of the 4-day-old rats, four male offspring per litter were reared and behavioural tests performed with one male pup per litter at the age of four months. Up to weaning, no clinical signs, body weight changes and no delays in the development markers pinna unfolding, righting reflex or tooth eruption and negative geotaxis were observed. Spontaneous motor activity in the form of locomotion, rearing and total activity was significantly increased in the exposed pups at the age of four months. In spatial learning tests, the pups showed a delayed reaction. At the age of 4.5 months, the time taken to reach a platform in the swimming maze was significantly longer on the 2nd day of the test compared with control animals. At the age of 5 months, the exposed animals were restless, made more mistakes and needed a longer time in order to find the 8 food pellets in the radial arm maze (Fredriksson et al. 1996). Thus, the results indicate effects on spontaneous and learned behaviours

Pregnant Sprague Dawley rats were exposed to **mercury vapour** at a concentration of 1.8 mg/m³ from gestation days 11 to 14 and 17 to 20 either for one hour (low dose group) or three hours (high dose group). No exposure took place on gestation days 15 and 16. Assuming a respiratory minute volume of 150 to 200 ml, a dose of 0.07 and 0.2 mg/kg body weight and day was calculated for the low and high concentration groups, respectively. No maternal toxicity occurred. No exposure-related effects on righting reflex, pinna unfolding, tooth eruption or negative geotaxis (on days 7, 8 or 9 after birth) were observed. After three months, the prenatally exposed young animals were hypoactive (reduced total activity, number and duration of rightings, locomotion). After 14 months, the deviations of the investigated parameters from those of the controls were slight and for the most part not significant. In spatial learning tests, the pups showed a delayed reaction and a reduced ability to adapt to a novel environment in the radial arm maze (when aged 4 months), but not in the circular swim maze (when aged 7 and 15 months) (Danielsson et al. 1993).

From gestation days 6 to 15, Long Evans rats were exposed two hours daily to **mercury vapour** at 0 or 4 mg/m³. On termination of the exposure, normal parturition took place, the dams were not investigated, and nerve functions were tested in the adult offspring. At the age of 140 to 168 days, six electrodes were implanted under anaesthesia into the brain of one male and one female per litter. Prenatal exposure to mercury vapour had no effect on nerve conduction velocity, nerve action potentials, cerebellar and cortical somatosensory evoked potentials, brainstem auditory and visually evoked responses of the offspring (Herr et al. 2004).

Female rats were exposed to **mercury vapour** at 0 or 2.5 mg/m³ six hours per day up to three weeks before mating and from gestation day 7 to 20. The number of live pups was significantly reduced. Ninety-six % of the pups of exposed mothers

died within the first four days after birth, none survived to weaning (Health Council Netherlands 2000).

Starting at week 3 to week 7 of pregnancy and continuing to the end of pregnancy (about week 22), ten pregnant squirrel monkeys were exposed to 1 mg/m^3 **mercury vapour**. All animals were exposed 5 days per week, of these one animal 24 hours per day, 4 animals 7 hours per day and 5 animals 4 hours per day. Ten animals were included as controls. There was a 60% incidence of abnormal pregnancy outcome in the exposed animals compared to 5% in the breeding colony. The incidence of abortion and neonatal mortality increased with exposure duration in the exposed animals, the birth weight of which was also decreased. The concentration of mercury in the brains of the offspring ranged between 0.2 and 0.3 μg/g brain and was thus about eight times less than in the maternal brains. Histopathological examination of the brains of the offspring revealed various effects. The brain sulci were irregular and not fully matured, especially in the frontal part of the cerebrum. Silver grains in the neurons and glial cells as well as in the ependyma cells (cells slining the ventricle and the *plexus choroideus*) were found. Heterotopic neurons were also found. This possibly indicates a disturbed neuronal migration (Berlin et al. 1992). No maternal toxicity was reported. It is also not clear whether, apart from the brain, other organs were also examined histopathologically. Furthermore, none of the findings were presented in tabular form, but only inadequately reported in the text. The conditions under which mortality was increased and body weight reduced in the offspring are therefore not transparent.

Starting at week 3 to week 7 of pregnancy, six pregnant squirrel monkeys were exposed to **mercury vapour** up to the end of pregnancy (about week 22 of pregnancy). One animal per group was exposed to 0.5 or 1 mg/m^3 mercury vapour 7 hours per day, and 2 animals per group to 0.5 or 1 mg/m^3 4 hours per day. The median maternal blood concentration for mercury was in the range of 0.025 to 0.18 μg/g blood and the estimated exposure to mercury ranged from 20 to 62 μg/day with cumulative mercury doses of 1304 to 4305 μg. No effects on weights at birth and body weight gain were reported. The 0.8 to 4-year-old offspring of both dose groups showed irregularities in steady performance or press durations, during transitions between regular and complex activites rin the lever-press tests(Newland et al. 1996).

Postnatal exposure and investigation

Newborn rats were exposed to 0.05 mg/m^3 **mercury vapour** either one or four hours per day from day 11 to 17 after birth, and their behaviour was investigated at the ages of two or four months. At the age of two months, daily exposure for four hours resulted in an increase in locomotion and general activity, but a decrease in rearing. At the age of four months, these rats were hypoactive in all three parameters. When the rats were exposed for only one hour a day, they showed, at the age of two months, no difference in behaviour to that of the control animals, but at the age of four months the same effects as in the high dose animals after two

months. In the spatial learning tasks, the rats exposed when young showed a learning retardation in the radial arm maze, whereas no differences occurred compared with controls in the circular swim maze (Fredriksson et al. 1992). This study is not relevant for assessing a hazard at the workplace, as the pups were not exposed until after birth.

Studies with inorganic mercury compounds

To date, developmental toxicity studies are available only for **mercury(II) chloride**. The results are given in Table 3.

Female mice received single intravenous injections of 0, 1.0, 2.0 or 2.5 mg Hg^{2+}/kg body weight in the form of **mercury(II) chloride** directly after mating, and the embryos were investigated 5 or 12 days later. In the dosed groups, the concentration of mercury in the blood of the dams was 0.05 ± 0.01, 0.22 ± 0.08 and 0.41 ± 0.12 µg/ml body weight on day 5 after administration, 0.09 ± 0.09, 0.06 ± 0.02 and 0.11 ± 0.06 µg/ml or 1.0, 2.0 and 2.5 mg Hg^{2+}/kg body weight on day 12, respectively. The number of embryos decreased dose-dependently and the number of abnormal embryos was increased (Kajiwara and Inouye 1992).

At different time points during pregnancy, Wistar rats received single intravenous injections of **mercury(II) chloride**. Mid-gestation the minimum effective teratogenic dose was 0.79 mg/kg body weight and day (maternal LD_{50} about 1 to 1.2 mg Hg^{2+}/kg body weight throughout pregnancy) and led in particular to hydrocephalus in 23% of the live foetuses. The uptake of Hg^{2+} by the foetuses of exposed mothers decreased sharply between gestation days 12 and 13. Teratogenic effects and kidney damage in the dams were similar on exposure before and after these gestation days. Investigations for skeletal and visceral changes revealed an increased incidence of foetuses with abnormalities; hydrocephalus was induced particularly from gestation days 8 to 14, haemorrhages from days 10 to 16, and skeletal retardations from days 10 to 14. An increased foetal mortality was not found in this study (Holt and Webb 1986). As only a single dose was administered, no NOAEL is obtained from this study. Its use for assessment is therefore limited.

Neurophysiological investigations were carried out in rats exposed orally to **mercury(II) chloride** during the pre- and/or postnatal development. Groups of pregnant Wistar rats were given mercury at concentrations of 0.4, 0.8 or 1.6 mg /kg body weight and day by gavage from gestation days 5 to 15, or during the same period and additionally during the 4 weeks of lactation, or the offspring for a further 8 weeks. At the age of 12 weeks, neurophysiological investigations with electrodes in the brain or tail nerve were carried out. Externally recognizable malformations occurred in none of the exposure groups. The final body weight of the exposed animals was slightly lower than in controls, though not dose-dependently and statistically not significant. No clinical signs or movement abnormalities were found. In the offspring exposed only prenatally, no significant changes were found in electrocorticogram, cortical evoked potentials, latency of certain evoked potential

Table 3 Developmental toxicity studies after administration of mercury chloride

Species, strain, number per group	Exposure	Findings	References
mouse, Kud:ddY, 5–10 ♀ per group	**single GD 0,** 0, 1.0, 2.0, 2.5 mg Hg^{2+}/kg body weight, intravenous; investigation on GD 5 or 12	investigation on GD 5: **at 1 mg Hg^{2+}/kg body weight dose dependent and above**: number of embryos decreased, number of abnormal embryos increased, number of normal egg cylinders decreased investigation on GD 12: **at 2 mg Hg^{2+}/kg body weight and above**: number of implantations decreased, foetal mortality increased, number of live foetuses decreased, foetal weight decreased	Kajiwara and Inouye 1992
rat, Wistar, 8–36 ♀ per group	**single GD 8, 10, 12, 14, 16 or 18**, 0, 0.79 mg Hg^{2+}/kg body weight, intravenous; investigation on GD 20	**0.79 mg Hg^{2+}/kg body weight**: number of abnormal foetuses on GD 12, 14, 16 increased, number of foetuses with hydrocephalus on GD 8–14 increased, number of foetuses with skeletal retardations on GD 10–14 increased, number of foetuses with haemorrhages on GD 10–16 increased	Holt and Webb 1986
rat, Wistar, 8 ♀ per group	**GD 5–15**, 0, 0.4, 0.8, 1.6 mg Hg^{2+}/kg body weight and day, gavage; investigation: 12 wks postpartum	neurophysiological study **1.6 mg Hg^{2+}/kg body weight**: offspring: no effects on body weight; relative liver, thymus and spleen weight increased (not significantly); electrophysiological parameters slightly reduced (not significant)	Papp et al. 2005
	GD 5–15, LD 2–28, 0, 0.4, 0.8, 1.6 mg Hg^{2+}/kg body weight and day, gavage; investigation: 12 weeks *post partum*	**up to 0.8 mg Hg^{2+}/kg body weight**: offspring: no effects **1.6 mg Hg/kg body weight:** offspring: no effect on body weight; relative liver, thymus and spleen weight increased (not significantly); electrophysiological parameters slightly reduced (not significantly)	

Table 3 (Continued)

Species, strain, number per group	Exposure	Findings	References
	GD 5–15, LD 2–28, offspring another 8 weeks, 0, 0.4, 0.8, 1.6 mg Hg^{2+}/kg body weight and day, gavage; investigation: 12 weeks *post partum*	**at 0.4 mg Hg^{2+}/kg body weight and above**: tail nerve: significant, conduction velocity decreased, refractory period increased **at 0.8 mg/kg body weight and above**: somatosensory electrocardiographic index decreased, latency of somatosensory evoked potential increased **1.6 mg Hg^{2+}/kg body weight**: (in relation to brain weight) relative liver weight increased, relative spleen weight increased, somatosensory + visual + auditory electrocorticographic index decreased, latency of somatosensory evoked potential lincreased	

Abbreviations: GD: gestation day; LD: lactation day

waves or in the conduction velocity of the tail nerve compared with the control group, although the values in the high dose group at 1.6 mg/m^3 were slightly, but statistically not significantly, reduced. As these reductions were significant after prenatal and postnatal exposure to 1.6 mg/m^3, the lack of statistical significance was attributed to the small number of animals (8 per group). The relative weights of liver, thymus and spleen in the offspring were slightly, but also statistically not significantly increased (Papp et al. 2005). Typical development markers in the offspring such as development of the pinna unfolding or opening of the eyes were not included in the investigation.

Summary: In a study with single intravenous injection of **mercury(II) chloride** (0.79 mg Hg^{2+}/kg body weight) investigations for skeletal and visceral changes were carried out. The incidence of abnormal foetuses was increased; hydrocephalus was induced especially from gestation days 8 to 14, haemorrhages from days 10 to 16 and skeletal retardation from days 10 to 14. No increased foetal mortality was found in this study (Holt and Webb 1986). In the studies available with inhalation exposure of rats to mercury vapour during pregnancy, no skeletal or visceral investigations were performed. It is therefore not possible to make any statement as to whether skeletal or visceral malformations occur after inhalation of mercury vapour.

The embryotoxicity or foetal toxicity of **mercury vapour** increases with exposure duration. In an inhalation study on prenatal developmental toxicity in rats (GD 6–15; 2 hours/day), resorptions were increased and litter size and weight at birth decreased only at 8 mg/m^3. The NOAEC was 2 mg/m^3 for maternal toxicity and

4 mg/m³ for the offspring at which level first signs of maternal toxicity occurred (Morgan et al. 2002). In an earlier investigation in rats, mercury vapour inhalation for 6 hours a day as well as over an extended period starting 3 weeks prior to mating and additionally from gestation days 7 to 20 showed that, already on gestation day 20, foetal mortality was increased at 2.5 mg/m³ and, postnatally, the number of live pups was reduced and the survival up to day 4 after birth greatly reduced (96%) (Health Council Netherlands 2000). In a total of ten squirrel monkeys, inhalation of mercury vapour at 1 mg/m³ during pregnancy with an increasing daily exposure duration (4, 7 or 24 hours per day) during pregnancy produced an increased incidence of abortions and neonatal mortality, and a decrease in weights at birth (Berlin et al. 1992). No mortality was reported, however, after 7-hour daily exposure of one monkey to mercury vapour at 1 mg/m³ (Newland et al. 1996).

Neurological changes: The histopathological examination of the brain of newborn squirrel monkeys after inhalation of mercury vapour at 1 mg/m³ (no exact data on daily exposure times) revealed various neurological effects. Impaired motor performance was observed from mercury vapour concentrations of 0.5 mg/m³ (Newland et al. 1996). Neurological changes at mercury vapour concentrations above 1 mg/m³ are reported in studies with rats; lower concentrations were not tested. A NOAEC for neurological impairment in prenatally exposed offspring cannot be derived from the available studies.

5.6 Genotoxicity

In the 1999 documentation, it was shown that inorganic mercury compounds are clearly clastogenic in vitro. The clastogenic effect is confirmed by a study in which mice received oral doses of **mercury(II) chloride**. This resulted in chromosome aberrations in bone marrow cells. The clastogenicity is caused by various mechanisms (inhibition of DNA repair or enzyme or protein systems participating in DNA replication, the formation of reactive oxygen species, or direct non-covalent interaction with DNA). It was as yet not possible to clarify the extent of qualitative or quantitative involvement of the individual processes. Nevertheless, a non-linear dose-response relationship is common to these effects. The genotoxic dose in animal studies was above 2 mg/kg body weight, and was thus at least 100 times above the dose obtained when the MAK value for mercury of 0.1 mg/m³ established in 1999 (about 15 µg/kg body weight and day at a respiratory volume of 10 m³ per shift, an assumed complete pulmonary absorption and a body weight of 70 kg) is observed (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German).

New data have appeared since then. These are described below.

Administered in its **chloride** or **nitrate** form, **mercury(II)** resulted in a concentration-dependent induction of micronuclei in V79 cells from 0.01 µM. CREST staining showed that the micronuclei were of both clastogenic and aneugenic

origin, with a slight prevalence of the aneugenic effect. Above 1 µM, mercury led to a concentration-dependent inhibition in the development of microtubules (Bonacker et al. 2004; Thier et al. 2003). The effect of mercury was not changed in the presence or absence of chelators like EDTA (Stoiber et al. 2004).

In the embryonal cells of Syrian hamsters, **mercury(II) chloride** treatment with 0, 10, 20, 30, 100 µM induced a significant increase in chromosome aberrations at 30 µM, with cytotoxicity occurring at 100 µM, (Akiyama et al. 2001).

An *in vivo* test on somatic mutations and recombinations in *Drosophila* (SMART, wing spot test) is available. In a concentration range of 0–50 µM, neither **mercury(II) chloride** nor methyl mercury chloride induced an increased number of mutations in *Drosophila* in the wing spot test. The toxicity of both substances was found to be high (Carmona et al. 2008).

5.7 Carcinogenicity

In the 1999 documentation (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German), carcinogenicity studies in rats and mice were described. The only animal study in rats with elemental mercury was not relevant for assessment on account of the intraperitoneal administration. Oral administration of **mercury(II) chloride** (5 mg/kg body weight and day) produced squamous cell papillomas in the forestomach of male rats . However, this dose level was above the MTD. In male mice, mercury chloride at 10 mg/kg body weight and day increased the number of renal tubular adenomas and carcinomas. The mechanism of action causing these tumours is unclear. There are no recent studies available.

5.8 Other effects

In neurobehavioural tests, metallothionein knockout mice reacted more sensitively to mercury exposure than wild type animals; this finding, however, did not correlate with the amount of mercury in the brain (Yoshida et al. 2004).

6 Manifesto (MAK value, classification)

In human studies and animal experiments, the target organs of repeated exposure to mercury are the kidneys and the nervous system.

MAK value/peak limitation. For mercury and inorganic mercury compounds biological monitoring is necessary to correlate exposure and inner burden in establishing a MAK exposure limit. The derivation of the previous MAK value of 0.1 mg/m^3 was therefore based on its correlation to the BAT value of 100 µg

mercury/L urine (see Documentation "Mercury, metallic mercury and inorganic mercury compounds" 1998*)*). In 2005, the BAT value was reduced from 100 µg mercury/L urine to 30 µg mercury/L urine (see Supplement "Mercury and its inorganic compounds", 2006, only available in German) or, taking into account creatinine excretion, changed to 25 µg mercury/g creatinine in 2007 (see Addendum, "Quecksilber und seine anorganischen Verbindungen", 2009 a, only available in German and Addendum, "Quecksilber und seine anorganischen Verbindungen", 2009 b, only available in German). The BAT value was derived on the basis of investigations in workers in the chloralkali industry exposed to elemental mercury vapour, where at a biological value of 25 µg mercury/g creatinine in humans no nephrotoxic or clinically relevant neurotoxic effect is to be expected. The new studies published since then are not in contradiction to this value. Therefore, in analogy to the reduction of the BAT value, the MAK value for mercury and inorganic mercury compounds is also reduced in accordance with the "preferred value approach" from 0.1 mg/m^3 to 0.02 mg/m^3 (calculated as mercury). Due to the systemic effects and the long half-life, classification in Peak Limitation Category II (excursion factor 8) has been retained.

Carcinogenicity. Already in 1999, the question of possible carcinogenic effects of elemental mercury could not be conclusively clarified from the epidemiological studies available at the time. In the case of inorganic mercury compounds, no human data were available on the subject. The only animal study with elemental mercury was not relevant for assessment due to the intraperitoneal route of administration selected. Oral administration of mercury(II) chloride to male rats induced squamous cell papillomas in the forestomach, but only above the MTD (maximum tolerated dose). In the male mouse, the number of renal tubular adenomas and carcinomas was increased. Owing to the lack of information on the carcinogenic mechanism of action, the relevance of these findings for humans is unclear. For this reason, mercury(II) chloride was classified in Carcinogen Category 3B. As both elemental and monovalent mercury are almost completely oxidized to divalent mercury in the organism, and all biological effects are attributed to this form (compare Section 3 here and the documentation of 1999 (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German), this classification also applied for elemental mercury and other inorganic mercury compounds.

As no new data on carcinogenicity are available, the new in vitro genotoxicity studies confirm the clastogenic effect in the high concentration range and an in vivo test in *Drosophila* is negative, the classification of mercury and inorganic mercury compounds in Category 3B for Carcinogenicity, valid up to now, has been retained.

Genotoxicity. As already presented in the documentation of 1999, inorganic mercury compounds are clearly clastogenic in vitro, and the clastogenic effect could be confirmed in one animal study. Clastogenicity is based on various mechanisms (inhibition of DNA repair or other enzyme or protein systems participating in DNA

replication, the formation of reactive oxygen species, or direct non-covalent interaction with DNA), however it has as yet not been possible to clarify the extent of qualitative or quantitative participation of the individual processes. Nevertheless, a non-linear dose-response relationship is common to these effects. The genotoxic dose level obtained in animal studies was more than 2 mg/kg body weight.

If the MAK value of 0.02 mg/m^3 for mercury is observed, the genotoxic dose level, after scaling to a concentration at the work place, lies at least 500 times higher than that taken up during exposure at the MAK value (about 3 µg/kg body weight and day at a respiratory volume of 10 m^3 per shift, an assumed complete pulmonary absorption and a body weight of 70 kg). Due to this large margin, the MAK value was provisionally retained in 1999 in spite of a suggested genotoxic effect in the high-dose range and the fact that there was no NOEL. Non-linear dose-response effects can be assumed therefore, mercury and inorganic mercury compounds are not classified in one of the categories for Germ Cell Mutagens.

The recent in vitro data confirm the clastogenic effect of mercury. With regard to in vivo experiments, apart from a negative test on somatic mutations and recombinations in *Drosophila* with mercury(II) chloride and methyl mercury chloride, new tests have not become available. The gap between the dose where genotoxic effects are found in animal experiments and the new MAK value of 0.02 mg mercury/m^3 is becoming greater. Mercury and inorganic mercury compounds have therefore still not been classified in one of the categories for Germ Cell Mutagens.

Absorption through the skin. Both in vitro and in vivo studies on the dermal penetration of mercury from aqueous solutions, contaminated soils and from the vapour phase are available. Studies with volunteers show that mercury is also absorbed through the skin from the vapour phase. Compared with the absorption by inhalation, the dermal uptake is however below 10%. From in vivo investigations with aqueous mercury(II) chloride solutions in guinea pigs, uptake rates in the range of 15 to 46 µg Hg/cm^2 and hour can be derived. This corresponds to an amount in the range of 30 to 92 mg for exposure of the hands and forearms (2000 cm^2) for one hour. However, in vitro results with pig skin show that most of the mercury absorbed through the skin accumulates in the skin and probably only a small part is systemically available. No data on mobilization of the mercury absorbed in the skin are available at present. Very similar values of 18 to 78 mg/2000 cm^2 and hour can be calculated from the penetration rates obtained in an in vitro study with human skin following exposure to a saturated aqueous mercury chloride solution. If one takes into account that, on exposure to a mercury concentration at the level of the MAK value of 0.02 mg/m^3, a daily body burden of only 0.2 mg mercury is obtained (assuming a respiratory volume of 10 m^3 per work shift and a 100% retention), the calculated quantities absorbed through the skin are so great that observance of the MAK value alone does not guarantee prevention of adverse effects on health. Therefore, mercury and inorganic mercury compounds are designated with an "H".

Sensitization. Since the documentation of 1999 (see Supplement "Mercury and inorganic mercury", 2001, a translation of the 1999 German), a number of additional findings on sensitization and contact allergic reactions to mercury or inorganic mercury compounds in humans have been published which confirm the contact sensitization of mercury and its inorganic compounds. Data on a respiratory sensitization are not available. Mercury and its inorganic compounds therefore continue to be designated with "Sh", but not with "Sa".

Prenatal toxicity. Epidemiological studies yield no consistent results. This is because several studies report an increased number of abortions and malformations in women exposed to mercury during pregnancy, though others do not (see Section 4.5). In studies with rats, indications for hydrocephalus and haemorrhages were obtained after intravenous injection of mercury chloride (0.79 mg Hg^{2+}/kg body weight); however, no skeletal or visceral investigations were performed in the inhalation studies with mercury vapour. Foetal mortality and postnatal mortality increasing with exposure duration was observed in rats and monkeys; however, no mortality in the offspring was found for one monkey after daily exposure to mercury vapour at 1 mg/m^3 for 7 hours during pregnancy. Behavioural changes were reported in monkeys at a mercury concentration as low as 0.5 mg/m^3. This means that the database is insufficient to obtain a reliable statement as to whether observance of the reduced MAK value (from 0.1 to 0.02 mg/m^3) presents a risk of prenatal toxicity or not. Thus, mercury and inorganic mercury compounds are classified in Pregnancy Risk Group D.

References

Akiyama M, Oshima H, Nakamura M (2001) Genotoxicity of mercury used in chromosome aberration tests. *Toxicol in vitro* 15: 463–467

Alanko K, Susitaival P, Jolanki R, Kanerva L (2004) Occupational skin disease among dental nurses. *Contact Dermatitis* 50: 77–82

Alcser KH, Brix KA, Fine LJ, Kallenbach LR, Wolfe RA (1989) Occupational mercury exposure and male reproductive health. *Am J Ind Med* 15: 517–529

Athavale PN, Shum KW, Yeoman CM, Gawkrodger DJ (2003) Oral lichenoid lesions and contact allergy to dental mercury and gold. *Contact Dermatitis* 49: 264–265

ATSDR (Agency for Toxic Substances and Disease Registry) (1999) Toxicological profile for mercury. US Department of Health and Human Services, March 1999, Atlanta, USA

Bartolome B, Cordoba S, Sanchez-Perez J, Fernandez-Herrera J, Garcia-Diez A (2000) Baboon syndrome of unusual origin. *Contact Dermatitis* 43: 113

Bast-Pettersen R, Ellingsen DG, Efskind J, Jordskogen R, Thomassen Y (2005) A neurobehavioral study of chloralkali workers after the cessation of exposure to mercury vapor. *Neurotoxicology* 26: 427–437

Belhadjali H, Youssef M, Zili J (2008) Systemic allergic dermatitis syndrome caused by mercury: a reply. *Contact Dermatitis* 59: 256

Bender HF, Beziel M, Krehenwinkel H, Lademann H, Münstedt R, Menig H, Will W, Nasterlack M (2006) Korrelation zwischen inhalativer Hg-Aufnahme und Hg-Ausscheidung. *Gefahrstoffe Reinhalt Luft* 66: 465–468

Berlin M, Hua J, Lögdberg B, Warfvinge K (1992) Prenatal exposure to mercury vapour: effects on brain development. In: Goering PL et al. Symposium Overview: toxicity assessment of mercury vapour from dental amalgams; *Fundam Appl Toxicol* 19: 319–329

Bonacker D, Stoiber T, Wang M, Böhm KJ, Prots I, Unger E, Thier R, Bolt HM, Degen GH (2004) Genotoxicity of inorganic mercury salts based on disturbed microtubule function. *Arch Toxicol* 78: 575–583

Carmona ER, Kossatz E, Creus A, Marcos R (2008) Genotoxic evaluation of two mercury compounds in the Drosophila wing spot test. *Chemosphere* 70: 1910–1914

Cebulska-Wasilewska A, Panek A, Zabinski Z, Moszczynski P, Au WW (2005) Occupational exposure to mercury vapour on genotoxicity and DNA repair. *Mutat Res* 586: 102–114

Cederbrant K, Gunnarsson LG, Marcusson JA (2000) Mercury intolerance and lymphocyte transformation test with nickel sulfate, palladium chloride, mercuric chloride, and gold sodium thiosulfate. *Environ Res* 84: 140–144

Cederbrant K, Hultman P (2000) Characterization of mercuric mercury (Hg2+)-induced lymphoblasts from patients with mercury allergy and from healthy subjects. *Clin Exp Immunol* 121: 23–30

Cheng TY, Tseng YH, Sun CC, Chu CY (2008) Contact sensitization to metals in Taiwan. *Contact Dermatitis* 59: 353–360

Chowdhury AR, Arora U (1982) Toxic effect of mercury on testes in different animal species. *Indian J Physiol Pharmacol* 26: 246–249

Chowdhury AR, Vachhrajani KD, Chatterjee BB (1985) Inhibition of 3β-hydroxy-delta-5-steroid-dehydrogenase in rat testicular tissue by mercuric chloride. *Toxicol Lett* 27: 45–49

Cordier S, Deplan F, Mandereau L, Hemon D (1991) Paternal exposure to mercury and spontaneous abortions. *Brit J Ind Med* 48: 375–381

Czarnobilska E, Obtulowicz K, Dyga W, Wsolek-Wnek K, Spiewak R (2009) Contact hypersensitivity and allergic contact dermatitis among school children and teenagers with eczema. *Contact Dermatitis* 60: 264–269

Danielsson BR, Fredriksson A, Dahlgren L, Gårdland AT, Olsson L, Dencker L, Archer T (1993) Behavioural effects of prenatal metallic mercury inhalation exposure in rats. *Neurotoxicol Teratol* 15: 391–396

Davidson PW, Myers GJ, Weiss B (2004) Mercury exposure and child development outcomes. *Pediatrics* 113: 1023–1029

Davis BJ, Price HC, O'Connor RW, Fernando R, Rowland AS, Morgan DL (2001) Mercury vapor and female reproductive toxicity. *Toxicol Sci* 59: 291–296

De Rosis F, Anastasio SP, Selvaggi L, Beltrame A, Moriani G (1985) Female reproductive health in two lamp factories: effects of exposure to inorganic mercury vapour and stress factors. *Brit J Ind Med* 42: 488–494

Di Pietro A, Visalli G, La Maestra S, Micale R, Baluce B, Matarese G, Cingano L, Scoglio ME (2008) Biomonitoring of DNA damage in peripheral blood lymphocytes of subjects with dental restorative fillings. *Mutat Res* 650: 115–122

Dunsche A, Frank MP, Lüttges J, Açil Y, Brasch J, Christophers E, Springer IN (2003 a) Lichenoid reactions of murine mucosa associated with amalgam. *Br J Dermatol* 148: 741–748

Dunsche A, Kästel I, Terheyden H, Springer IN, Christophers E, Brasch J (2003 b) Oral lichenoid reactions associated with amalgam: improvement after amalgam removal. *Br J Dermatol* 148: 70–76

Elghany NA, Stopford W, Bunn WB, Fleming LE (1997) Occupational exposure to inorganic mercury vapour and reproductive outcome. *Occup Med* 47: 333–336

Erfurth EM, Schütz A, Nilsson A, Barregard L, Skerfving S (1990) Normal pituitary hormone response to thyrotrophin and gonadotrophin releasing hormones in subjects exposed to elemental mercury vapour. *Brit J Ind Med* 47: 639–644

Ericson A, Källén B (1989) Pregnancy outcome in women working as dentists, dental assistants or dental technicians. *Int Arch Occup Environ Health* 61: 329–333

Farahat SA, Rashed LA, Zawilla NH, Farouk SM (2009) Effect of occupational exposure to elemental mercury in the amalgam on thymulin hormone production among dental staff. *Toxicol Ind Health* 25: 159–167

Fredriksson A, Dahlgren L, Danielsson B, Eriksson P, Dencker L, Archer T (1992) Behavioural effects of neonatal metallic mercury exposure in rats. *Toxicology* 74: 151–160

Fredriksson A, Dencker L, Archer T, Danielsson BRG (1996) Prenatal coexposure to metallic mercury vapour and methylmercury produce interactive behavioural changes in adult rats. *Neurotoxicol Teratol* 18: 129–134

Friberg L, Skog E, Wahlberg JE (1961) Resorption of mercuric chloride and methyl mercury dicyandiamide in guinea-pigs through normal skin and through skin pretreated with acetone, alkylarylsulphonate and soap. *Acta Derm Venereol* 41: 40–52

Frumkin H, Letz R, Williams PL, Gerr F, Pierce M, Sanders A, Elon L, Manning CC, Woods JS, Hertzberg VS, Mueller P, Taylor BB (2001) Health effects of long-term mercury exposure among chloralkali plant workers. *Am J Ind Med* 39: 1–18

Gale TF, Ferm VH (1971) Embryopathic effects of mercuric salts. *Life Sci* 10: 1341–1347

García-Menaya JM, Cordobés-Durán C, Bobadilla P, Lamilla A, Moreno I (2008) Baboon syndrome: 2 simultaneous cases in the same family. *Contact Dermatitis* 58: 108–109

Gier-Stuschke B, Reinhardt W, Rettenmeier AW (2006) Membranöse Glomerulonephritis with nephrotischem Syndrom durch berufliche Quecksilberbelastung. *Arbeitsmed Sozialmed Umweltmed* 4: 626–627

Hanf V, Forstmann A, Costea JE, Schieferstein G, Fischer I, Schweinsberg F (1996) Mercury in urine and ejaculate in husbands of barren couples. *Toxicol Lett* 88: 227–231

Health Council Netherlands (2000) Committee for Compounds toxic to reproduction. Mercury and its compounds; evaluation of the effects on reproduction, recommendation for classification. The Hague: Health Council of the Netherlands, 2000; publication No. 2000/05OSH, http://gezondheidsraad.nl/sites/default/files/00@05OSH.PDF

Heidam LZ (1984) Spontaneous abortions among dental assistants, factory workers, painters, and gardening workers: a follow up study. *J Epidemiol Commun Health* 38: 149–155

Heine G, Schnuch A, Uter W, Worm M (2004) Frequency of contact allergy in German children and adolescents patch tested between 1995 and 2002: results from the Information Network of Departments of Dermatology and the German Contact Dermatitis Research Group. *Contact Dermatitis* 51: 111–117

Herr DW, Chanda SM, Graff JE, Barone SS Jr., Beliles RP, Morgan DL (2004) Evaluation of sensory evoked potentials in Long Evans rats gestationally exposed to mercury (Hg0) vapor. *Toxicol Sci* 82: 193–206

Holt D, Webb M (1986) The toxicity and teratogenicity of mercuric mercury in the pregnant rat. *Arch Toxicol* 58: 243–248

Hursh JB, Clarkson TW, Miles EF (1989) Percutaneous resorption of mercury vapor by man. *Arch Environ Health* 44: 120–127

Iwata T, Sakamoto M, Feng X, Yoshida M, Liu XJ, Dakeishi M, Li P, Qiu G, Jiang H, Nakamura M, Murata K (2007) Effects of mercury vapor exposure on neuromotor function in Chinese miners and smelters. *Int Arch Occup Environ Health* 80: 381–387

Jayaprakash K (2009) Mercury vapour inhalation and its effect on glutathione peroxidans in goldsmiths exposed occupationally. *Toxicol Ind Health* 25: 463–465

Khan AT, Atkinson A, Graham TC, Thompson SJ, Ali S, Shireen KF (2004) Effects of inorganic mercury on reproductive performance of mice. *Food Chem Toxicol* 42: 571–577

Kajiwara Y, Inouye M (1986) Effects of methylmercury and mercury chloride on preimplantation mouse embryos in vivo. *Teratology* 33: 231–237

Kajiwara Y, Inouye M (1992) Inhibition of implantation caused by methylmercury and mercuric chloride in mouse embryos in vivo. *Bull Environ Contam Toxicol* 49: 541–546

Laeijendecker R, Dekker SK, Burger PM, Mulder PG, Van Joost T, Neumann MH (2004) Oral lichen planus and allergy to dental amalgam restorations. *Arch Dermatol* 140: 1434–1438

Lamperti AA, Printz RH (1973) Effects of mercuric chloride on the reproductive cycle of the female hamster. *Biol Reprod* 8: 378–387

Lauwerys R, Roels H, Genet P, Toussaint G, Bouckaert A, De Cooman S (1985) Fertility of male workers exposed to mercury vapor or to manganese dust: a questionnaire study. *Am J Ind Med* 7: 171–176

Lauwerys R, Bonnier C, Evrard P, Gennart JP, Bernard A (1987) Prenatal and early postnatal intoxication by inorganic mercury resulting from the maternal use of mercury containing soap. *Human Toxicol* 6: 253–256

Lee IP, Dixon RL (1975) Effects of mercury on spermatogenesis studied by velocity sedimentation cell separation and serial mating. *J Pharmacol Exp Ther* 194: 171–181

Lee JY, Yoo JM, Cho BK, Kim HO (2001) Contact Dermatitis in Korean dental technicians. *Contact Dermatitis* 45: 13–16

Lerch M, Bircher AJ (2004) Systemically induced allergic exanthem from mercury. *Contact Dermatitis* 50: 349–353

Loftenius A, Skogland A, Ekstrand J, Hovmark A, Möller E (1999) No evidence for specific in vitro lymphocyte reactivity to HgCl2 in patients with dental amalgam-related contact lesions. *J Oral Pathol Med* 28: 364–370

Morgan DL, Chanda SM, Price HC, Fernando R, Liu J, Brambila E, O'Connor RW, Beliles RP, Barone Jr. S (2002) Disposition of inhaled mercury vapor in pregnant rats: maternal toxicity and effects on developmental outcomes. *Toxicol Sci* 66: 261–273

Mosel F, Eitschberger H, Sulkowski M, Hirner AV, Rettenmeier AW (2006) Verteilung von Quecksilber in Blut, Urin and Stuhl in einem beruflich Hg-belasteten Kollektiv (Distribution of mercury in blood, urine and faeces in a collective occupationally exposed to Hg) (German). *Arbeitsmed Sozialmed Umweltmed* 41: 562–563

Nagar RN, Bhattacharya L (2001) Effect of mercuric chloride on testicular activities in mice, musculus albinos. *J Environ Biol* 22: 15–18

Newland MC, Warfvinge K, Berlin M (1996) Behavioral consequences of in utero exposure to mercury vapor: alterations in lever-press durations and learning in Squirrel monkeys. *Toxicol Appl Pharmacol* 139: 374–386

Oh CK, Jo JH, Jang HS, Kim MB, Kwon YW, Kwon KS (2003) An unusual case of mercurial baboon syndrome from metallic mercury in a broken industrial barometer. *Contact Dermatitis* 49: 309–310

Oppel T, Schnuch A (2006) Häufigste Auslöser allergischer Kontaktekzeme (Most frequent inducers of allergic contact eczemas) (German). *Dtsch Med Wochenschr* 131: 1584–1589

Özkaya E (2008) An unusual case of mercurial baboon syndrome: lasting seasonal attacks in a retired metalworker. *Contact Dermatitis* 58: 107–108

Özkaya E, Mirzoyeva L, Otkür B (2009) Mercury-induced systemic allergic dermatitis caused by "white precipitate" in a skin lightening cream. *Contact Dermatitis* 60: 61–63

Papp A, Nagymajtényi L, Vezér T (2005) Subchronic mercury treatment of rats in different phases of ontogenesis: functional effects on the central and peripheral nervous system. *Food Chem Toxicol* 43: 77–85

Pezelj-Ribarić S, Prpić J, Miletić I, Brumini G, Soskić MS, Anić I (2008) Association between oral lichenoid reactions and amalgam restorations. *J Eur Acad Dermatol Venereol* 22: 1163–1167

Prem AS, Vachhrajani KD Bose M, Dutta KK (1992) Action of mercuric chloride during one cycle of seminiferous epithelium in the rat. *Bull Environ Contam Toxicol* 48: 865–868

Rowland (1992) Reproductive effects of mercury vapor. In: Goering PL et al. Symposium Overview: toxicity assessment of mercury vapour from dental amalgams. *Fundam Appl Toxicol* 19: 319–329

Rowland I, Davies M, Grasso P (1977) Biosynthesis of methylmercury compounds by the intestinal flora of the rat. *Arch Environ Health* 32: 24–28

Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ (1994) The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. *Occup Environ Med* 51: 28–34

Sartorelli P, Montomoli L, Sisinni AG, Cioni F, Barabesi L, Bussani R, Sartorelli E (2002) Studio in vitro dell'assorbimento transcutaneo del mercurio inorganico dal terreno solido (In vitro study on the transcutaneous absorption of inorganic mercury in solid medium) (Italian). *Med Lav* 93: 279–285

Shimada A, Kishimoto M, Sawada M, Morita T, Yoshida M, Satoh M, Tohyama C (2004) Oxidative stress and basement membrane changes in the acute pulmonary toxicity induced by mercury exposure. *Toxicol Appl Pharmacol* 197: 307

Seidenari S, Giusti F, Pepe P, Mantovani L (2005) Contact sensitization in 1094 children andergoing patch testing over a 7-year period. *Pediatr Dermatol* 22: 1–5

Sikorski R, Juszkiewicz T, Paszkowski T, Szprengier-Juszkiewicz T (1987) Women in dental surgeries: reproductive hazards in occupational exposure to metallic mercury. *Int Arch Occup Environ Health* 59: 551–557

Skog E, Wahlberg JE (1962) The effect of alkylaryl-sulfonate and soap on the percutaneous resorption in guinea-pigs of mercuric chloride and methyl mercury dicyandiamide. *Acta Derm Venereol* 42: 17–20

Skowronski GA, Turkall RM, Abdel-Rahman MS (2000) In vitro penetration of soil-aged mercury through pig skin. *J Toxicol Environ Health* 61: 189–200

Söderström S, Fredriksson A, Dencker L, Ebendal T (1995) The effect of mercury vapour on cholinergic neurons in the fetal brain: studies on the expression of nerve growth factor and its low- and high-affinity receptors. *Dev Brain Res* 85: 96–108

Stoiber T, Bonacker D, Böhm KJ, Bolt HM, Thier R, Degen GH, Unger E (2004) Disturbed microtubule function and induction of micronuclei by chelate complexes of mecury(II). *Mutat Res* 563: 97–106

Suter KE (1975) Studies on the dominant-lethal and fertility effects of the heavy metal compounds methylmercuric hydroxide, mercuric chloride, and cadmium chloride in male and female mice. *Mutat Res* 30: 365–374

Suzuki K, Matsunaga K, Umemura Y, Ueda H, Sasaki K (2000) 2 cases of occupational dermatitis due to mercury vapor from a broken sphygmomanometer. *Contact Dermatitis* 43: 175–177

Tan SW, Meiller JC, Mahaffey KR (2009) The endocrine effects on mercury in humans and wildlife. *Crit Rev Toxicol* 39: 228–269

Thier R, Bonacker D, Stoiber T, Böhm KJ, Wang M, Unger E, Bolt HM, Degen GH (2003) Interaction of metal salts with cytoskeletal motor protein systems. *Toxicol Lett* 140-141: 75–81

Umweltbundesamt (2002) Umwelt-Survey 1998, Band III: Human-Biomonitoring, Stoffgehalte in Blut und Urin der Bevölkerung in Deutschland. *WaBoLu* Heft 1/02, ISSN 0175-4211 http://www.umweltbundesamt.de/sites/default/files/medien/publikation/long/2104.pdf

US EPA (2007) Elemental Mercury. Toxicity and exposure assessment for childrens health (TEACH) chemical summary, 9/21/2007, http://www.epa.gov/TEACH/chem_summ/index.html

Uter W, Geier J, Pfahlberg A, Effendy I (2002) The spectrum of contact allergy in elderly patients with and without lower leg dermatitis. *Dermatology* 204: 266–272

Valentine-Thon E, Müller K, Guzzi G, Kreisel S, Ohnsorge P, Sandkamp M (2006) LTTMELISA is clinically relevant for detecting and monitoring metal sensitivity. *Neuro Endocrinol Lett* 27 Suppl 1: 17—24 (Erratum in: Neuro Endocrinol Lett. 2007 Oct; 28(5): iii)

Valentine-Thon E, Schiwara HW (2003) Validity of MELISA for metal sensitivity testing. *Neuro Endocrinol Lett* 24: 57–64

Wastensson G, Lamoureux D, Sällsten G, Beuter A, Barregard L (2006) Quantitative tremor assessment in workers with current low exposure to mercury vapor. *Neurotoxicol Teratol* 28: 681–693

Wen L, Yin J, Ma DL, Lanier B (2007) Baboon syndrome induced by mercury – first case report in China. *Contact Dermatitis* 56: 356–357

Westphal GA, Schnuch A, Schulz TG, Reich K, Aberer W, Brasch J, Koch P, Wessbecher R, Szliska C, Bauer A, Hallier E (2000) Homozygous gene deletions of the glutathione-S-transferases M1 and T1 are associated with thimerosal sensitization. *Int Arch Occup Environ Health* 73: 384–388

WHO (World Health Organization) (2003) Elemental mercury and inorganic mercury compoands: human health aspects. Concise international chemical assessment document Nr 50, WHO, Geneva

Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R (2003). Patch testing in children, adults, and the elderly: influence of age and sex on sensitization patterns. *Pediatr Dermatol* 20:119–123

Wong L, Freeman S (2003) Oral lichenoid lesions (OLL) and mercury in amalgam fillings. *Contact Dermatitis* 48: 74–79

Worm M, Aberer W, Agathos M, Becker D, Brasch J, Fuchs T, Hillen U, Höger P, Mahler V, Schnuch A, Szliska C (2007) Epikutantestung bei Kindern – Empfehlungen der Deutschen Kontaktallergiegruppe (DKG) (Patch testing in children – Recommendations of the German Contact Allergy Group) (German). J Dtsch Dermatol Ges 5: 107–109 (Corrigendum: *J Dtsch Dermatol Ges* 5, 541 (2007)

Wünscher U, Roschig M, Friese KH, Hoffmann P (1991) Percutaneous resorption of mercury vapor by rats. *Arch Toxicol* 65: 257–259

Yoshida M (2002) Placental to fetal transfer of mercury and fetotoxitiy. *Tohoku J Exp Med* 196: 79–88

Yoshida M, Watanabe C, Satoh M, Yasutake A, Sawada M, Ohtsuka Y, Akama Y, Tohyama C (2004). Susceptibility of metallothionein-null mice to the behavioral alterations caused by exposure to mercury vapour at human-relevant concentration. *Tox Sci* 80: 69–73

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