Inorganic mercury/ elemental mercury

Toxicological overview

Key Points

Kinetics and metabolism

- The main route of exposure to elemental mercury and inorganic mercury is inhalation and ingestion, respectively
- Following inhalation of elemental mercury or ingestion of inorganic mercury compounds, they are distributed to all tissues but mainly accumulate in the kidney. Elemental mercury may readily cross the blood-brain barrier
- Elimination of elemental mercury and inorganic mercury compounds predominantly occurs via the urine and faeces.

Health effects of acute exposure

- Inhalation of elemental mercury may cause respiratory effects (cough, dyspnoea), central nervous system effects (tremor, irritability), renal damage (proteinuria, haematuria, acute renal failure), gastrointestinal disturbances (stomatitis, nausea, diarrhoea) and cardiovascular effects (hypertension and tachycardia)
- Ingestion of inorganic mercury compounds may affect the digestive tract (metallic taste, vomiting, swollen gums, salivation, abdominal pain, diarrhoea), renal damage (oliguria, anuria, acute renal failure), cardiovascular effects (tachycardia, hypertension) and skin/eye effects (acrodynia, burning eyes and conjunctivitis)

Health effects of chronic exposure

- Inhalation of elemental mercury vapour may cause neurotoxicity (fatigue, tremor, headaches, depression, hallucinations), nephrotoxicity (proteinuria and enzymuria) and effects on the oral cavity (stomatitis, sore gums and oral mucosa ulcers)
- Ingestion of inorganic mercury compounds may cause neurotoxicity (irritability, weakness, photophobia, muscle twitching, confusion or dementia), digestive tract effects (swollen gums, salivation, diarrhoea or abdominal pain) or renal failure
- IARC classified elemental mercury and mercury compounds as category 3 carcinogens i.e. not classifiable as to the carcinogenicity to humans

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Toxicological Overview

Summary of Health Effects

Following an acute exposure to elemental mercury vapour via inhalation, respiratory effects such as cough, dyspnoea, chest tightness, bronchitis and decreased pulmonary function may occur. Cognitive, personality, sensory or motor disturbances may also arise, including tremor, irritability, hallucinations, muscle weakness and headaches. Due to the accumulation of mercury in the kidneys, acute renal failure indicated by proteinuria, haematuria and oliguria is commonly reported. Acute inhalation of elemental mercury may also cause GI effects such as stomatitis, abdominal pain, vomiting, diarrhoea and ulceration of the oral mucosa, as well as cardiovascular effects such as hypertension and tachycardia.

Inorganic mercury compounds are highly irritating to the GI tract and an acute ingestion may cause a metallic taste, abdominal pain, vomiting, diarrhoea and necrosis of the intestinal mucosa, possibly leading to circulatory collapse and death. Ulceration of the mouth, lips, tongue and GI tract may also occur. If patients survive damage to the GI tract, acute renal failure may occur within 24 hours of ingestion. Hypertension and tachycardia have also been reported following ingestion of inorganic mercury compounds.

Acute dermal exposure to elemental mercury vapour can cause erythematous and pruritic skin rashes, reddening and peeling of skin on palms of feet and hands associated with acrodynia, and contact with soluble inorganic mercury compounds may cause irritation, vesiculation and contact dermatitis.

Chronic exposure to elemental mercury vapour via inhalation may cause neurotoxicity such as decreased psychomotor skills and neuropsychological symptoms including fatigue, tremor, headaches, depression, irritability, and hallucinations. Nephrotoxicity including proteinuria and increase urinary enzyme excretion was observed following occupational exposure to elemental mercury, as well as stomatitis, sore gums and ulceration of the oral mucosa.

Following chronic ingestion of inorganic mercury compounds irritability weakness, insomnia, muscle twitching, swollen gums, excess salivation, anorexia and abdominal pain may occur.

There is little convincing evidence that exposure to mercury causes chromosomal damage or other mutagenic effects.

IARC have classified elemental mercury and inorganic mercury compounds as category 3 carcinogens i.e. not classifiable as to carcinogenicity to humans.

Conflicting evidence regarding the incidence of spontaneous abortion following inorganic mercury exposure has been presented. Some studies have reported a higher incidence of reproductive failures (spontaneous abortions, still births, congenital malformations) and irregular, painful and haemorrhagic menstrual disorders in occupationally exposed women compared to unexposed women.

Kinetics and metabolism

The two forms of mercury, namely elemental and inorganic mercury have different biological properties hence are discussed separately.

Elemental mercury

The absorption of mercury is largely dependent on the form. The predominant route of exposure for elemental mercury is inhalation. After inhalation, approximately 80 % of mercury vapour crosses the alveolar membrane and is rapidly absorbed into the blood. Liquid elemental mercury is poorly absorbed (approximately 0.01 %) from the gastrointestinal tract probably due to its conversion to divalent mercury and binding to sulfhydryl groups [1-3]. Dermal exposure to elemental mercury vapour may also occur to some extent, contributing to approximately 2.6 % of the absorbed dose. Absorption via the olfactory nerves has also been proposed although quantitatively this is a minor pathway [3].

Absorbed elemental mercury is rapidly distributed to all tissues, although it accumulates to the greatest extent in the kidney, reaching between 50 and 90 % of the body burden [1, 3]. It reaches peak levels in all tissues within 24 hours, apart from the brain where peak levels are only reached after 23 days. Due to the high lipophilicity, elemental mercury readily passes the blood-brain barrier and the placenta. [3].

Following inhalation and absorption into the blood, elemental mercury vapour undergoes oxidation in the red blood cells to form divalent mercury, which predominantly exists as a non-diffusible form and binds to albumin and globulins. Oxidation may also occur in the liver and lungs, although it may occur in most other tissues to a lesser extent. In the brain and fetus, elemental mercury may be oxidised and thereby trapped as the divalent form does not cross the blood-brain barrier or the placenta as readily [3].

Elimination of elemental mercury predominantly occurs through the urine and faeces, although some may be excreted in sweat, expired air or saliva, with the half-life being approximately 1-2 months. After an acute exposure, urinary excretion accounts for approximately 13 % of the total body burden, this increasing to approximately 58 % after chronic exposure. Elemental mercury may be exhaled as mercury vapour or excreted in breast milk [2, 3].

Inorganic mercury

For inorganic mercury, the predominant route of exposure is ingestion [3]. In humans, approximately 5 – 10 % of inorganic mercury in food is absorbed after ingestion [2]. Following inhalation, the rate of absorption of inorganic mercury aerosols is dependent on particle size but on average, approximately 10 % is absorbed, as most particles will be deposited in the upper respiratory tract [1, 3].

The extent to which inorganic mercury is transported across the intestinal tract is largely dependent on its solubility and its dissociation in the lumen. Mercuric compounds are more readily absorbed than mercurous forms due to their solubility [3].

Inorganic mercury is distributed to all tissues following absorption, but due to the poor lipid solubility only a small fraction crosses the blood-brain barrier and the placenta. As is the case for elemental mercury, the largest systemic deposition of inorganic mercury occurs in the kidney [2].

The main pathway of excretion of inorganic mercury is via the urine and faeces, with the half life of approximately 1-2 months [1, 3]. Elimination of inorganic mercury from the blood and brain is a biphasic process encompassing an initial rapid elimination phase followed by a

slower phase [3]. Inorganic mercury may also be reduced to form elemental mercury which is exhaled as elemental mercury vapour or excreted in the breast milk [2, 3].

Sources and route of exposure

Mercury occurs naturally and is widely distributed in the environment owing to natural and anthropogenic processes. The major natural sources of mercury in the environment are degassing from the earth's crust, emissions from volcanoes and evaporation from water bodies [1]. Elemental mercury is also released into the air following man-made activities such as mining ore containing mercury, burning fossil fuels and incinerating waste. Mercury also enters the environment from fertilizers, fungicides and from solid waste i.e. thermometers or electrical switches [2].

Mercury may be detected in ground water in the range of 5 – 100 ng L^{-1}. Naturally occurring elemental mercury in both ground and surface water is less than 0.5 μg L^{-1}. Mercury in drinking water is not considered a major source of exposure except when significant pollution occurs [4].

The environmental fate of mercury in the soil is largely dependent on its form. The most common forms are mercury compounds which bind to soil organic matter, adsorb to mineral surfaces or precipitate as compounds of sulphur under reducing conditions [5]. However, some mercury salts are almost insoluble in water and therefore are unlikely to have significant mobility in soil [2]. Elemental mercury occurs in soil due to anthropogenic activities, although it may also form naturally as a by-product from microbial activity. The release of elemental mercury and other volatile mercury compounds from soil may be important in the cycling of mercury and may explain increased concentrations of mercury near to mercury-containing ore bodies [5].

Elevated concentrations of mercury in soil may lead to an increase in the mercury content in plants such as carrots, lettuce, mushrooms and apples, which, if grown in contaminated soil, may accumulate mercury. However, few data are available regarding the relationship between mercury concentration in the soil and the concentration in fruit and vegetables [5].

The general public is predominantly exposed to elemental mercury via inhalation of its vapour from amalgam used in dental fillings or from accidental spillages following breakages of thermometers, barometers or electrical switches [1, 6].

People undergo exposure to inorganic mercury by ingestion due to the use of mercury salts in herbal remedies [3]. Dermal exposure may also occur, as mercury salts were commonly used for their antiseptic, fungicidal and bactericidal properties [3]. In addition, the use of skin-lighteners can result in significant exposure due to dermal absorption [1].

Occupational exposure to mercury may be a major source of exposure. Individuals working in the production of electrical equipment, thermometers or barometers, those working in chemical processing plants or construction may all be exposed to elemental mercury vapour via inhalation or inorganic mercury [6]. Dentists and dental assistants involved with dental amalgam may also be exposed to elemental mercury due to inhalation and to a lesser extent by skin contact [3, 6]. Workplace exposure limits (WELs) for mercury and inorganic mercury compounds have been derived in the UK. The long-term exposure limit (LTEL) is 0.025 mg m^{-3} (8 hour time weighted exposure (TWA) reference period). No data were available for the short-term exposure limits (STEL) (15 minute reference period) [7].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

The major target organs of elemental mercury-induced toxicity are the central nervous system and the kidneys. The cardiovascular and respiratory system, GI tract and the skin are also affected at higher concentrations. Similarly, the target organs following ingestion of inorganic mercury are the kidneys and the central nervous system [1, 8].

Inhalation

Most data on the toxicity of mercury following inhalation refer to elemental mercury, as other forms, such as inorganic mercury, do not pose a significant risk via this route of exposure [6]. Following inhalation, the major target organs are the central and peripheral nervous system, and the kidneys, although at high concentrations respiratory, cardiovascular and gastrointestinal effects may also occur [6, 8].

Following an acute exposure to elemental mercury vapour, respiratory effects such as cough, dyspnoea and chest tightness have been reported, as well as bronchitis and bronchiolitis with interstitial pneumonitis, airway obstruction, and decreased pulmonary function. In severe cases pulmonary oedema, respiratory distress, and fibrosis may occur. Patients commonly develop respiratory insufficiency [1, 3, 6, 8, 9]. Such effects have been reported following exposure to 1.1 – 44 mg m^{-3} elemental mercury [9]. Inorganic mercury compounds have also been reported to cause respiratory effects such as shortness of breath or pulmonary oedema [3]

The central nervous system is one of the most sensitive targets following exposure to elemental mercury vapour, which may cause cognitive, personality, sensory or motor disturbances [3]. The effects may include tremor, irritability, nervousness, memory loss, hallucinations and neuromuscular changes such as muscle atrophy and muscle weakness, headaches and decreases in cognitive function [1, 3].

The kidneys are a major target organ following exposure to elemental mercury vapour due to the relatively high accumulation of mercury in the kidneys. High concentrations (not stated) have been reported to result in mild transient proteinuria, haematuria, oliguria, acute renal failure and degeneration of the proximal convoluted tubules [1, 3, 6].

Gastrointestinal effects have been reported in humans following acute inhalation of elemental mercury vapour. A classic symptom of mercury toxicity is inflammation of the oral mucosa, known as stomatitis, sometimes accompanied with excessive salivation and difficulty in swallowing. Other gastrointestinal effects including abdominal pain, nausea, diarrhoea, sore gums and ulceration of the oral mucosa may also occur following inhalation of elemental mercury vapour, although few studies report the concentration of mercury at which such symptoms arise [1, 3, 6].

Hypertension and tachycardia have both been reported following inhalation of high concentrations of elemental mercury, as well as hepatocellular effects, hepatomegaly and

central lobular vacuolation. Hypertension and tachycardia may also arise following exposure to inorganic mercury [3, 6].

Elemental mercury vapour has been reported to cause erythematous and pruritic skin rashes, reddening and peeling of skin on palms of feet and hands associated with acrodynia, burning eyes and conjunctivitis [3].

Acute exposure to elemental mercury vapour may produce 'metal fume fever', which is characterised by fatigue, fever and elevated leukocyte count [6].

Ingestion

Most data on the toxicity of mercury following ingestion refer to inorganic mercury compounds, as elemental mercury via ingestion does not, in general, cause serious effects [8].

Following ingestion, the major target organs are the GI tract, kidneys, cardiovascular system and the skin [3, 8, 9].

Ingestion of inorganic mercury salts such as mercuric chloride is highly irritating to the GI tract. One of the earliest symptoms is a metallic taste, followed by gastric pain and vomiting. As the compound passes into the lower GI tract abdominal pain, diarrhoea and necrosis of the intestinal mucosa may occur, possibly leading to circulatory collapse and death [9]. Ingestion of mercuric chloride may also lead to blistering and ulceration of the lips and tongue, oropharyngeal pain and ulceration of the GI tract [3, 6]. In contrast, ingestion of mercurous chloride appears to cause les severe GI effects, although individual case studies have reported nausea, vomiting, swollen gums, excess salivation, diarrhoea, anorexia and abdominal pain following the ingestion of unknown concentrations of mercurous chloride [3, 6]. Ingestion of elemental mercury results in negligible absorption and therefore exert little effect on the GI tract [6].

The kidney is a critical target organ following the ingestion of inorganic mercury compounds. If patients survive GI tract damage following exposure to mercury salts, oliguria, anuria, necrosis of the proximal tubule epithelium and acute renal failure may occur within 24 hours of the ingestion of mercuric chloride prior to death [1, 9].

Tachycardia and hypertension have been reported following the ingestion of mercuric chloride and mercurous chloride [6]. In addition, tachycardia has been reported secondary to severe pneumonitis after acute exposure to mercury vapour [9].

Limited data are available regarding the respiratory effects following ingestion of inorganic mercury. Pulmonary oedema and shortness of breath have been reported following ingestion of mercuric chloride (dose not stated) [6].

Ingestion of elemental mercury may cause erythematous and pruritic skin rashes, reddening and peeling of skin on palms of feet and hands associated with acrodynia, burning eyes and conjunctivitis [3].

Ingestion of mercuric chloride may cause jaundice and elevation of liver enzymes [3, 6].

Dermal / ocular exposure

Dermal exposure to elemental mercury vapour may cause erythematous and pruritic skin rashes, reddening and peeling of skin on palms of feet and hands associated with acrodynia, burning eyes and conjunctivitis [3].

Soluble inorganic mercury compounds, in particular mercuric chloride, are irritating to the skin and mucous membranes. Exposure to 1 – 5 % may cause irritation, vesiculation, contact dermatitis and corrosion of the skin [3, 9]. Insoluble compounds are not immediately irritating but irritation may slowly develop as the compound is absorbed and ionised in tissues [9].

Amalgam filings have occasionally been shown to cause dermatitis on the face. In addition, dermatitis caused by allergy to elemental mercury has been described in dental personnel [1].

Neurological effects have been reported following dermal exposure to inorganic mercury [8].

Animal and In-Vitro Data

Inhalation

Inhalation of elemental mercury vapour (1 – 1.1 mg m^{-3} for 1 – 30 hours resulted in death of rabbits [8]. Mice, guinea pigs and rats inhaling elemental mercury vapour died of pulmonary oedema (concentration unknown) [6, 8].

Cardiovascular effects were also noted in animals. Cellular degeneration with necrosis of the heart tissue was observed in rabbits following exposure to 28.8 mg m^{-3} elemental mercury vapour for 4 – 30 hours. In the same study, gastrointestinal effects were noted, ranging from mild pathological changes to significant cellular degeneration and necrosis of the colon, as well as hepatic effects ranging from moderate pathological changes (unstated) to severe liver necrosis [6]. Rabbits also showed signs of renal effects ranging from cellular degeneration to tissue destruction and necrosis following inhalation of 28.8 mg m^{-3} elemental mercury vapour for 2 – 30 hours [6].

Ingestion

Ingestion of elemental mercury results in negligible absorption and therefore exerts little toxicological effect [6].

Few data are available regarding the toxicity of inorganic mercury following oral exposure.

Rats administered a single gavage dose of mercuric chloride (7.4 or 9.2 mg kg^{-1}) showed no differences in body weight or liver weight compared to controls although LDH activity was significantly decreased at both doses [6].

Renal toxicity was observed in rats and mice following acute exposure to mercuric chloride. Male and female rats were exposed to mercuric chloride (0.93 – 14.8 mg kg^{-1} day^{-1}) by gavage for five days a week. There was a significant increase in the kidney weights in groups exposed to 1.9 mg kg^{-1} $day^{-1}$and higher. Tubular necrosis occurred in rats exposed to 3.7 mg

kg^{-1} day^{-1} and higher, the severity increasing in a dose-dependent manner. An increase in urinary levels of alkaline phosphatase, AST and LDH was also observed in such groups [6].

Mice given a single dose of 10 mg kg^{-1} day^{-1} mercuric chloride by gavage showed minor renal tubular damage and rapid regeneration of the tubular epithelium [6].

Neurotoxicity was observed in rats following a single exposure to mercuric chloride (0.74 mg kg^{-1}) given by gavage and subcutaneously. Leakage of dye into the brain tissue, 12 hours after the single dose, demonstrated that the blood-brain barrier had been breached [6].

Health Effects of Chronic / Repeated Exposure

Human Data

General toxicity

Chronic exposure to mercury may affect the central nervous system, GI tract, kidneys, oral cavity, lungs, eyes, reproductive tract and skin.

Inhalation

Long-term exposure to elemental mercury vapour may cause neurotoxicity. Decreased psychomotor skills and neuropsychological symptoms, such as fatigue, tremor and headaches have been reported [3, 8]. As the exposure increases, the frequency and magnitude of muscle tremor increase and there are behavioural changes such as depression, memory loss, irritability and hallucinations [1, 8]. The peripheral nervous system may also be affected following chronic exposure to mercury vapour, resulting in reduced sensory and motor nerve function. No concentrations were reported [1, 8].

Effects on the central nervous system are generally considered to be the most sensitive indicator of toxicity of metallic mercury vapour [1, 2]. Studies on those occupationally exposed have shown a fairly consistent pattern of effects such as irritability, excitability, insomnia, tremor, decreased nerve conduction velocity, fatigue, short term memory deficits and depression. These studies, involving chlor-alkali workers, suggest a lowest observed adverse effect level (LOAEL) of 15-30 $\mu g\ m^{-3}$ metallic mercury expressed as an 8 hour concentration [2].

Occupational exposure to elemental mercury vapour may also result in kidney damage, indicated by proteinuria, increased urinary excretion of β-galactosidase, transferrin, β2-microglobulin or albumin, and proximal tubular and glomerular changes [1, 6]. Slight changes in blood enzymes indicative of renal tubular effects were seen in workers with an estimated exposure to mercury vapour (based on the levels of mercury excreted in the urine) of 15 $\mu g\ m^{-3}$ [2].

Effects of chronic inhalation of elemental mercury on the cardiovascular system are equivocal as studies have reported differing results. Two studies reported that after exposure to mercury (0 – 0.27 and 0.075 mg m^{-3}) for more than 6 or 7 years no effects were observed on blood pressure. In contrast, workers exposed to 0.03 mg m^{-3} for at least 5 years showed signs of palpitations and cardiovascular reflex responses. Exposure to elemental mercury vapour has also been reported to cause hypertension and tachycardia, although concentrations were not stated [6].

Ingestion

Few data are available regarding the toxicity of inorganic mercury following chronic exposure. Dementia, colitis and renal failure has been reported following ingestion of mercurous chloride-containing laxative for between 6 and 25 years [8].

Children treated with products containing mercurous chloride (such as teething powders) many years ago exhibited signs of irritability, weakness, insomnia, photophobia, muscle

twitching or confusion. Such treatments no longer exist [3, 8]. Gastrointestinal effects such as swollen gums, excess salivation, anorexia, diarrhoea or abdominal pain were also seen in children treated with mercurous chloride [6]

Genotoxicity

Data from 14 studies of cytogenetic effects, such as sister chromatid exchange, micronucleus formation, chromosomal aberrations, aneuploidy and polyploidy in peripheral blood lymphocytes of individuals exposed to elemental mercury or mercury compounds were inconclusive. Overall, such monitoring studies have provided little convincing evidence that exposure to mercury causes chromosomal damage [3, 10].

Carcinogenicity

There was inadequate evidence in humans for the carcinogenicity of mercury and mercury compounds hence IARC have classified elemental mercury and inorganic mercury compounds as category 3 carcinogens. i.e. not classifiable as to carcinogenicity to humans. [10].

Reproductive and developmental toxicity

Several studies showed that chronic inhalation of elemental mercury had no effect on female fertility. Menstrual cycle disorders were reported to be more frequent in women occupationally exposed to elemental mercury [1, 3].

Data regarding the incidence of spontaneous abortion following inorganic mercury exposure are conflicting. Several studies reported a slightly elevated incidence of spontaneous abortions in women working in smelting plants or dental practices, whereas others did not find a correlation [1, 6]. One study carried out in female dentists and dental assistants reported a higher incidence of reproductive abnormalities (spontaneous abortions, still births, congenital malformations) and irregular, painful and haemorrhagic menstrual disorders than in unexposed women. This study, however, was criticised for erroneous interpretation of data [6]. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that there was no evidence that occupational exposure to mercury during pregnancy in modern dental practices was harmful [11].

Some studies have reported that various forms of mercury reach the fetus via the placenta. Mercury vapour penetrates the placental barrier easier than inorganic mercury although whether the placenta concentrates mercury is unclear. Following inhalation of mercury, comparable levels of mercury were found in mother, foetus and placenta [12].

It has been reported that dentists or dental assistants who were occupationally exposed to metallic mercury below the threshold limit value had higher concentrations of metallic mercury in the placenta and fetal membranes compared with unexposed women. However, even in non-exposed women, the concentration of mercury in maternal blood increased by 46 % during pregnancy [12].

No information was available regarding the developmental/reproductive toxicity of inorganic mercury following oral exposure [8].

Males exposed to elemental mercury vapour in an occupational setting showed no association between mercury exposure and decreased fertility, or with increased rates of major malformations or serious childhood disease in their offspring [1].

Animal and In-Vitro Data

Inhalation

Respiratory effects were seen following chronic exposure to elemental mercury vapour. Rats exposed to 1 mg m^{-3} mercury vapour for 100 hours per week for six weeks showed signs of lung congestion, whereas rats exposed to 3 mg m^{-3} for 3 hours a day, five days a week for 12 – 42 weeks showed no significant changes [6].

Cardiovascular effects were also noted in animals. Mild to moderate pathological changes in the hearts of rabbits was observed following exposure to 0.86 - 6 mg m^{-3} elemental mercury vapour for 2 – 12 weeks [6].

No gastrointestinal changes were observed in rabbits exposed to 6 mg m^{-3} for seven hours a day, five days a week for up to 11 weeks, although hepatic changes were reported ranging from moderate pathological changes to marked cellular degeneration and necrosis [6].

In rats, slight degenerative changes were seen in the renal tubular epithelium following inhalation of 3 mg m^{-3} mercury vapour for three hours a day five days a week for 12-42 weeks [6].

Ingestion

Studies in animals have indicated that nephrotoxicity is the most sensitive endpoint following repeated exposure to inorganic mercury compounds [2]. Sub-acute studies (6 months) in rats given mercuric chloride orally, indicated a NOAEL of 0.23 mg kg^{-1} day^{-1}. There was evidence of nephrotoxicity at 0.46 mg kg^{-1} day^{-1} and higher dose levels. Studies have also been reported in the Brown Norway rat, a species prone to the development of mercuric chloride-induced glomerulonephritis. Some evidence of effects were seen following oral doses of 3 mg mercuric chloride once a week for 60 days; this was considered to be the LOAEL (the daily dose was estimated to be around 0.3 mg kg^{-1} day^{-1} [2].

Respiratory effects such as forceful and laboured breathing, nose bleeds and other unspecified breathing difficulties were observed in rats following dietary exposure to 2.2 mg kg^{-1} day^{-1} mercuric chloride for three months [6].

Several studies reported cardiovascular effects following oral exposure to inorganic mercury. Exposure of rats to 28 mg kg^{-1} day^{-1} mercuric chloride for 180 days in drinking water resulted in hypertension and a decrease in cardiac contractility but did not affect heart rate. In contrast, a different strain of rat exposed to 7 mg kg^{-1} day^{-1} mercuric chloride in drinking water for 360 days as hypertension and increased cardiac contractility were observed, as well as decreased baroreceptor reflex sensitivity [6].

Genotoxicity

No experimental data were available on the genotoxicity of elemental mercury.

Studies with mercuric chloride gave conflicting results [10]. Single-strand DNA breaks have been reported following exposure of cultured mice embryo cells and Chinese hamster ovary cells to mercuric chloride. Other studies reported the induction of gene mutations in mouse lymphoma cells and DNA damage in rat and mouse fibroblasts. In contrast, mercuric chloride did not induce chromosome aberrations in human lymphocytes *in vitro* [1]. No *in-vivo* data are available. However, the data from the carcinogenicity studies do not suggest that inorganic mercury compounds have significant mutagenic potential.

Carcinogenicity

There is inadequate evidence in experimental animals for the carcinogenicity of metallic mercury and limited evidence for the carcinogenicity of mercuric chloride [10]. Following oral exposure to mercuric chloride (1.9 or 3.7 mg kg^{-1} day^{-1} for two years) male rats showed an increased incidence of forestomach hyperplasia compared to controls [6]. Other studies reported that rats given oral mercuric chloride (up to 5 mg kg^{-1} day^{-1}) showed a significant increase in squamous cell papillomas of the forestomach and thyroid follicular cell adenomas and carcinomas compared with controls. However, the forestomach tumours did not progress to malignancy and were thought to arise from direct irritation of the tissue [2]. Similar studies on mice treated with up to 10 mg kg^{-1} day^{-1} showed a significant dose-related trend in renal tubular adenomas and adenocarcinomas [8]. However, such kidney tumours occurred at doses that were also nephrotoxic and would be expected to arise by a non-genotoxic mechanism [2].

Reproductive and developmental toxicity

Limited data are available regarding the reproductive toxicity of inorganic mercury. Male mice injected with single doses of mercuric chloride (1 mg kg^{-1}) showed decreased fertility with normal fertility resuming after approximately 2 months. Rats treated with intraperitoneal doses of 0.05 – 0.1 mg kg^{-1} mercuric chloride over 90 days showed a gradual alteration in testicular tissue, such as a decrease in seminiferous tubular diameter, spermatogenic cell counts and Leydig cell nuclear diameter [1].

An increase in fetal resorptions in hamsters occurred followed a single oral exposure to mercuric chloride (31.4 mg Hg kg^{-1}) [8]. Several studies have reported the occurrence of spontaneous abortions following exposure to elemental mercury vapour or inorganic mercury compounds. Decreased fetal weight and increased number of malformations i.e. cardiac abnormalities also occurred [1].

Several studies have investigated effects on ovulation in female hamsters. Animals were injected with mercuric chloride (3 – 12.8 mg kg^{-1}), resulting in the inhibition of ovulation or follicular maturation [1].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.