# Mercuric chloride poisoning: symptoms, analysis, therapies, and autoptic findings. A review of the literature

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**ABSTRACT**

Among mercury-related intoxications, the re-emerging of mercuric chloride poisoning has been recently described in literature. Only sparse data, reporting the clinical symptoms, the anatomo-pathological findings, the analytical procedures or the treatment have been published and no exhaustive analysis of all these factors exists in literature. The classic symptoms associated with toxicity of mercuric chloride is a combination of renal, gastrointestinal (GI) and central nervous system (CNS) damages, eventually leading to death. Fatalities related to exposure to mercuric chloride have been reported since the nineteenth century. To date, there have been 45 published cases in the medical literature in which the intoxication or the death is attributed to mercuric chloride. In this review, we will describe the modern medical treatments, with particular attenztion to the developments of the lasts two decades, in order to provide an exhaustive description of the clinical symptoms, the *post-mortem* findings, and the analytical procedures to act out when mercuric chloride intoxication occurs. The analysis of the data obtained permitted us to accurately describe all the organs and apparatus involved in mercuric chloride intoxication. The target organs were the kidneys, the GI tract and the CNS. A description of the analytical procedures for the determination of mercuric chloride in biological materials, to carry out *in vivo* and in *post-mortem* samples has also been described.

Accepted 16 May 2019

**KEYWORDS**

Mercury chloride; mercury poisoning; forensic toxicology; mercury intoxication

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## Introduction

Mercuric chloride is an inorganic molecule that can be found in the form of white, rhombic crystals, granules, or powder. Historically known as corrosive sublimate, it has been widely used as an antiseptic agent (Dart 2004), especially for the treatment for syphilis, with a particularly high frequency at the end of the nineteenth century (Clarkson and Magos 2006; Norn et al. 2008). Nowadays, it is no longer used for medicinal purposes because of its toxicity and the availability of newer and more effective treatments.

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Mercuric chloride has a relative molecular mass of 271.52 Dalton, a melting point of 277 °C, and a boiling point of 302 °C. It has a vapor pressure of 0.1 kPa at 136.2 °C and a water solubility of 28.6 g/L, which increases to 476 g/L in boiling water; its solubility in alcohol is of 263 g/L (WHO 2003). Mercuric chloride is currently used as a catalyst or reagent in several chemical reactions, and to a lesser extent as a disinfectant or pesticide (Worth et al. 1984). Potential sources of mercuric chloride intoxications are represented by mercuric chloride-containing stool preservatives (Seidel 1980), Ayurvedic medicines remedies (Indian herbo-metallic preparations) (Kew et al. 1993; Kamath et al. 2012; Kumar et al. 2015), mainly containing *Rasasindura* – a preparation consisting of mercuric sulfide, mixed with honey, milk, butter, or ghee. The latter, which are not subject to Food and Drug Administration (FDA) and European Medicine Agency (EMA) regulation are easily available without prescription (Young-Jin 2011).

Mercury toxicity, as a result, is a significant clinical entity, as it is ubiquitous in the environment and poses serious risk to human health. The pathology of mercury toxicity in humans includes direct damage to tissues and enzyme function as well as indirect damage as a result of oxidative stress.

Despite this chemical compound being no longer employed in medicine, reports of intoxications and deaths, due to its use, have been reported in the last years.

In this review, we will summarize the toxicokinetics, mechanisms of toxicity, clinical features, *post-mortem* findings, diagnosis, and management of mercuric chloride poisoning.

## Methods

The National Center for Biotechnology Information (PubMed) and Science Direct Scopus databases were searched by using the search terms “mercuric chloride,” “mercuric bichloride,” “corrosive sublimate” combined with the keywords “poison,” “intoxication,” “overdose,” “succimer,” “DMPS,” “DMSA,” and “BAL,” in title and/or abstract. This search identified 521 articles, which were then screened based on their abstract to identify their relevance in respect of the toxicokinetics, mechanisms of toxicity, clinical features, diagnosis, *post-mortem* findings, and management of mercuric chloride poisoning; 54 articles were relevant.

References of identified articles were manually examined to find additional relevant studies including non-peer-reviewed resources. All articles describing intoxications due to other mercury compounds (e.g. methylmercury) were excluded. This search provided eleven additional relevant articles.

This review has a number of strengths that include the breadth of the studies, which span the globe, as well as the hand search and scan of reference lists for the identification of all relevant studies. Despite our efforts to thoroughly and fairly evaluate the existing literature, it must be noted that this review includes studies that were published over a time frame of over a hundred years and that only 45 mercuric chloride poisoning papers (consisting of 174 cases) were identified, thus the amount of the examined literature is relatively limited (Table 1).

## Results

### Toxicokinetics

#### Absorption

Ingestion appears to be the most common route of exposure, but mercuric chloride can also be absorbed following dermal or intravenous exposure. The absorption has been demonstrated with numerous animal models. Piotrowski et al. (1992), by using whole-body retention data, estimated a mercuric chloride absorption equal to 3–4, 8.5, and 6.5%, respectively, for single oral doses of 0.2–12.5 mg/kg body weight, 17.5 mg/kg body weight, and 20 mg/kg body weight, respectively, in rats. Furthermore, by using whole-body retention data to assess absorption, an estimated absorption of 20–25% was calculated from single oral doses of 0.2–20.0 mg mercuric chloride/kg body weight in mice (Nielsen and Andersen 1990).

The rate of oral absorption of mercuric mercury compounds in laboratory rodents has been shown to be related to age, intestinal pH, and diet (Kostial et al. 1978; Endo et al. 1990). Indeed, young mice absorbed 38% of the orally administered mercuric chloride, whereas adult mice absorbed only 1% of the dose on standard diets. It has also been hypothesized that the nutritional status may contribute to the intestinal absorption of mercuric chloride, through competition with nutritionally essential divalent cations (e.g. $Cu^{2+}$ and $Zn^{2+}$) that may be characterized by insufficient body storage (WHO 2003). However, absorption of mercuric chloride may be increased at high doses due to its corrosive action on the GI tract.

On one hand, mercuric chloride has been reported to be absorbed through the skin of animals (up to 6–8%) (Silberberg et al. 1969); on the other hand, there is evidence of dermal absorption in humans, which is provided by clinical case-reports in which intoxication was related to dermal application of ointments containing mercuric chloride. Urine samples collected from young women, who used skin lightening creams containing up to 10% mercuric chloride, were found to have a mean mercury concentration of 109 μg/L, compared with 6 μg/L for urine samples collected from women who had discontinued cream use and 2 μg/L for women who had never used them (Barr et al. 1973). The degree of dermal absorption varies depending on the concentration of mercury, skin integrity, and lipid solubility of the substance. With significant dermal exposures to mercuric chloride, skin absorption may be difficult to distinguish from concomitant absorption *via* other routes, such as ingestion (Young-Jin 2011).

Specific information on the absorption of inhaled mercuric chloride is lacking, although an absorption of approximately 40% has been estimated in dogs (Theissen et al. 1994).

#### Distribution

After its absorption, mercury distributes widely to all tissues, predominantly the kidneys, the liver, the spleen, and the central nervous system (CNS). This data mainly derives from animal studies. Many authors found the kidney, and in a lower percentage the liver, to have the highest mercury levels following repeated oral exposure to mercuric chloride in mice

**Table 1.** Summary of previously published cases related to mercuric chloride intoxication.

| First author/s (year of publication) | Country | Study type (number of participants) | Age and sex | Dose (g or mL) | Route of administration | Manner | Outcome |
|---|---|---|---|---|---|---|---|
| Mack (1846) | Canada | Case report ($N = 1$) | 40 M | N/R | Oral | Homicide | Died |
| Gundrum (1913) | US | Case report ($N = 1$) | N/R | 0.5 g | Vaginal douche | Accidental | Died |
| Millar (1916) | Scotland | Case report ($N = 1$) | 27 F | 8.75 g | Vaginal douche | Accidental | Died |
| Harmon (1928) | US | Case series ($N = 4$) | 35 F/ 40 M/ 49 M/ 60 M | 5–6 g | Intravenous | Accidental | 4 died |
| Longcope and Luetscher (1949) | US | Retrospective study ($N = 61$) | N/R | 0.5–20 g | N/R | N/R | 2 died 59 survived |
| Troen et al. (1951) | US | Retrospective study ($N = 54$) | Between 2 and 60 (25 M, 29 F) | 0.33–4 g | N/R | 44 suicidal intent 10 N/R | 9 died 45 survived |
| Montuschi (1953) | UK | Case report ($N = 1$) | 37 M | 2 g | Oral | Suicide attempt | Survived |
| Doolan et al. (1953) | US | Case report ($N = 1$) | 28 F | N/R | Oral | N/R | Survived |
| Augustine (1956) | US | Case report ($N = 1$) | 27 - | 1 g | Oral | Suicide attempt | Survived |
| Sanchez-Sicilia et al. (1963) | US | Case series ($N = 7$) | 51 F/ 35 M/ 64 F/ 30 M/ 41 M/ 20 F/ 55 F | -/10 g/-/5 g/-/1.5 g/- | 7 Oral | 2 accidental 1 suicide 3 suicide attempt 1 N/R | 2 died/5 survived |
| Klendshoj and Rejent (1966) | US | Case report ($N = 1$) | 48 F | 4.5 g | Oral | N/R | Died |
| Gingell et al. (1967) | UK | Case report ($N = 1$) | 68 F | 250 ml, 1/500 | Peritoneal lavage | Accidental | Survived |
| Steentoft (1972) | Denmark | Case report ($N = 1$) | 53 M | N/R | Oral | N/R | Died |
| Lowenthal et al. (1974) | US | Case report ($N = 1$) | 35 M | 4–8 g | Oral | Suicide attempt | Survived |
| Pesce et al. (1977) | US | Case report ($N = 1$) | 18 M | 1.5 g | Oral | Suicide attempt | Survived |
| Meyboom (1978) | Netherlands | Case report ($N = 1$) | 59 F | N/R | Peritoneal lavage | Accidental | Died |
| Cross et al. (1979) | Scotland | Case series ($N = 3$) | N/R | N/R | Peritoneal lavage | Accidental | 2 died 1 survived |
| Pusey et al. (1979) | UK | Case series ($N = 2$) | 50 F/ 61 F | N/R | Peritoneal lavage | Accidental | 2 Survived |
| Murphy et al. (1979) | UK | Case report ($N = 1$) | N/R | N/R | Oral | Suicide | Died |
| Seidel (1980) | US | Case series ($N = 4$) | 2 F/4 M/4 M/5 M | -/0.43 g/-/-/ | Oral | Accidental | 4 survived |
| Winek et al. (1981) | US | Case report ($N = 1$) | 66 F | N/R | Oral | N/R | Died |
| Samuels et al. (1982) | Canada | Case report ($N = 1$) | 19 months M | N/R | Oral | Accidental | Survived |
| Giunta et al. (1983) | Italy | Case report ($N = 1$) | - F | 2.5 g | Oral | Accidental | Survived |
| Lai et al. (1983) | China | Case report ($N = 1$) | 64 M | N/R | Peritoneal lavage | Accidental | Survived |
| Stack et al. (1983) | UK | Case report ($N = 1$) | 23 months M | N/R | Oral | Accidental | Survived |
| Laundy et al. (1984) | UK | Case report ($N = 1$) | 53 F | 500 ml, 1/500 | Peritoneal lavage | Accidental | Died |
| Worth et al. (1984) | UK | Case report ($N = 1$) | 29 M | N/R | Oral | Accidental | Survived |
| Nadig et al. (1985) | Germany | Case report ($N = 1$) | 19 F | 3 g | Oral | N/R | Survived |
| Dittmann and Pribilla (1985) | Germany | Case report ($N = 1$) | 19 M | 5 ml | Intravenous | Suicide | Died |
| Sauder et al. (1988) | France | Case report ($N = 1$) | 27 M | 6 g | Oral | Suicide | Died |
| Kostyniak et al. (1990) | US | Case report ($N = 1$) | 70 F | 1.425 g | Oral | Suicide attempt | Survived |
| McLauchlan (1991) | UK | Case report ($N = 1$) | 23 F | 7 g | Oral | Suicide | Died |
| Kang-Yum and Oransky (1992) | US | Case series ($N = 1$) | N/R | 7 g | Oral | Suicide | Died |
| Suzuki et al. (1992) | Japan | Case report ($N = 1$) | - F | 0.9 g | Oral | Suicide attempt | Survived |
| Toet et al. (1994) | Netherlands | Case report ($N = 1$) | N/R | N/R | Oral | N/R | Survived |
| Singer et al. (1994) | US | Case report ($N = 1$) | N/R | 0.675 g | Oral | N/R | Survived |

(*continued*)

**Table 1.** Continued.

| First author/s (year of publication) | Country | Study type (number of participants) | Age and sex | Dose (g or mL) | Route of administration | Manner | Outcome |
|---|---|---|---|---|---|---|---|
| Kurka et al. (1996) | Czech Republic | Case report ($N = 1$) | N/R | N/R | Oral | N/R | Survived |
| Yoshida et al. (1997) | Japan | Case report ($N = 1$) | 26 F | 0.9 g | Oral | Suicide attempt | Survived |
| Pelclová et al. (2002) | Czech Republic | Case report ($N = 1$) | 21 M | N/R | Dermal | Accidental | Survived |
| Wang et al. (2007) | US | Case report ($N = 1$) | 22 M | 37 g | Oral | Suicide attempt | Survived |
| Sabbe et al. (2008) | Belgium | Case report ($N = 1$) | 36 F | N/R | Oral | Suicide | Died |
| Triunfante et al. (2009) | Portugal | Case report ($N = 1$) | 39 M | 50 g | Oral | Suicide | Died |
| Lino et al. (2009) | Australia | Case report ($N = 1$) | 36 M | N/R | Oral | Suicide | Died |
| Verma et al. (2010) | India | Case report ($N = 1$) | 2 M | N/R | Oral | Accidental | Survived |
| Beasley et al. (2014) | New Zealand | Case report ($N = 1$) | 19 F | 2–4 g | Oral | Suicide attempt | Survived |

N/R not reported.
*Committee on the Safety of Medicines (case No 54948).

for a period of 2–8 weeks (Nielsen and Andersen 1990; Theissen et al. 1994).

The brain has substantially lower mercury levels after exposure to mercuric chloride; however, retention is the longest in this tissue. Furthermore, mercury can also accumulate in human hair following oral exposure to mercuric chloride (Suzuki et al. 1992).

Mercuric chloride has a limited ability to cross the placental barrier. This was shown by an intravenous study in pregnant mice (Inouye and Kajiwara 1990), in which, following intravenous doses of mercuric chloride (1.4 mg/kg) on a random day between days 9 and 17 of pregnancy, mercuric chloride was transferred inefficiently to the fetus, being blocked almost completely by the fetal membrane. The mercury accumulated in the placenta and the yolk sac, but not in the amnion or the fetal body. Histochemical studies have demonstrated that mercuric chloride is blocked in the proximal wall of the yolk sac (Inouye and Kajiwara 1990).

### *Metabolism*

The available evidence indicates that the metabolism of mercuric chloride is similar for both humans and animals. Once absorbed, mercuric chloride enters into an oxidation–reduction cycle. It is suggested that the absorbed divalent cation deriving from the exposure to mercuric chloride compounds can, in turn, be reduced to the metallic or monovalent form and released as exhaled mercury vapor (WHO 2003). In fact, rats and mice, pre-treated parenterally with mercuric chloride, exhale metallic mercury vapor (Clarkson and Rothstein 1964; Dunn et al. 1981a). The amount of released mercury increases upon treatment with ethanol (Dunn et al. 1981b). This increase suggests that glutathione reductase is responsible for mercuric ion reduction (Williams et al. 1982).

### *Elimination*

Mercuric chloride ions are excreted through the kidneys by both glomerular filtration and tubular secretion and in the gastrointestinal (GI) tract by transfer across gut mesenteric vessels into feces.

The total-body half-life of mercuric chloride ions is estimated at approximately 30–60 d (Magos 1988). Data obtained from laboratory mammals on excretion are limited, but they seem to suggest that excretion is species- and dose-dependent. Age is an important factor in the elimination of mercury in rats following mercuric chloride exposure, with younger rats showing significantly higher retention rates than older rats. Mercuric chloride can be also excreted in breast milk. To conclude, there are no data suggesting that the route of exposure affects the elimination of the substance through the body.

Small amounts of the compound are reduced to elemental mercury vapor and volatilized through the skin and the lungs. Elimination from the blood and the brain is hypothesized to be a biphasic process with an initial rapid phase in which the decline in the body burden is associated with high levels of mercury being cleared from the tissues, followed by a slower phase of mercury clearance from the same tissues

(Takahata et al. 1970). An even longer terminal-elimination phase is also possible because of persistent accumulation of mercury, primarily in the brain (Takahata et al. 1970).

More information is needed to fully explain the elimination of mercuric chloride with breast milk. Sundberg et al. studied the elimination of radiolabelled mercuric chloride in lactating and non-lactating mice exposed to intravenous injection of mercuric chloride (Sundberg et al. 1998). A three-compartment pharmacokinetic model was used to fit the data. The study was designed to provide additional information on the speciation of mercury in breast milk and the differences between organic and inorganic mercury migration into milk.

### *Mechanisms of toxicity*

From a pathophysiological standpoint, the pervasive disruption of normal cell physiology by mercuric chloride is believed to derive from its avid covalent binding to sulfur, with mercuric chloride replacing the hydrogen ion in the body's ubiquitous sulfhydryl groups. Mercuric chloride also reacts with phosphoryl, carboxyl, and amide groups, resulting in a widespread dysfunction of enzymes, membranes, transport mechanisms, and structural proteins. Mercuric chloride is being investigated in a variety of cellular alterations, including oxidative stress, microtubule disruption, protein and DNA synthesis, impairment of synaptic transmission, impairment of the immune response, disruption in calcium homeostasis, and cell membrane integrity. This can cause metabolic acidosis, and, in the early phases of toxicity, it can cause death due to metabolic acidosis, vasodilatation, and shock (Winship 1985). The above-mentioned alterations may be acting alone or in combination (ATSDR 1999; Young-Jin 2011).

Due to mercuric chloride being able to accumulate itself in all tissues, the clinical manifestations of mercury toxicity involve multiple organ systems with varying features and intensity. In particular, the necrosis of the GI mucosa and proximal renal tubules, which occurs shortly after mercury poisoning, is thought to result from the direct oxidative effect of mercuric ions. An immune mechanism is thought to be involved in the membranous glomerulonephritis and acrodynia associated with the use of mercurial preparations (Becker et al. 1962).

The progression of renal toxicity has been widely studied in animal models. This process includes initial degenerative changes in the epithelial cells of the proximal tubules, such as nuclear swelling, increased eosinophilia/basophilia, vacuolization, and cellular hypertrophy. In the early stages, these degenerative changes are accompanied by tubular regeneration. Occasionally, when there is minor toxic damage, only regenerative changes are observed. As the lesions progress, tubular dilation, desquamation of the epithelial cells, and thickening of the tubular basement membrane are described. Necrosis, inflammation, fibrosis, and atrophy of the tubules and glomerular changes (i.e. hypercellularity and thickening of the glomerular basement membrane) have been also observed (ATSDR 1999).

Recent studies have highlighted the potential cardiovascular effects of mercuric chloride intoxication. The mechanism that may predispose individuals to cardiovascular diseases depends on the production of free radicals or the inactivation of several antioxidative mechanisms in which the liver plays a major role (Aguado et al. 2013). Toxicity has been associated with the generation of reactive oxygen species (ROS), which are an inevitable product of respiration in aerobic organisms. An increase of ROS usually leads to oxidative stress, which results in cellular damage in numerous organs and tissues (Méndez-Armenta et al. 2011). ROS are known to be generated in large amounts under inflammatory conditions. Their production is counteracted by an arsenal of antioxidative defense species, which include vitamins (C and E), glutathione, zinc, selenium, metallothioneins, and specific enzymes (Sundaresan and Subramanian 2003). The principal ROS-scavenging enzymes are catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase.

Basing on these assumptions, Lee et al. conducted an experimental study on cultured mice hepatocytes, consisting in the use of innovative glycoproteins, such as Zanthoxylum piperitum DC (ZPDC). This glycoprotein increases the activity of hepatic antioxidant enzymes and reduces glutathione production (Lee et al. 2014). This experimental study appears to support the effective employment of ZPDC glycoprotein as a natural compound able to counteract mercury-chloride-induced hepatotoxicity with minimal side effects. Despite these positive and potentially useful findings, further in-depth studies are necessary.

Nowadays, the possibility of transportation of mercury through the human placenta barrier and its consequences have been studied by many authors (Gundacker et al. 2010). Significantly higher mercury levels in fetal blood compared to maternal blood have been observed; thus, an active placental transport to the fetus, possibly by amino acid transporters, can be hypothesized (Stern and Smith 2003). However, despite these studies, the mechanistic basis of mercury influx, retention, and efflux across the human placenta barrier remains largely unknown.

In recent years, biomolecular studies have been performed in order to evaluate the interaction between mercury compounds and serum proteins to understand the biochemical basis of the toxicological effects of mercurial species (Li et al. 2007; Yun et al. 2013). Through these studies, which have investigated the stoichiometry and thermodynamics interaction of inorganic mercury ($Hg^{2+}$) with human serum albumin (HSA), two types of binding sites for mercury species were identified. The primary binding sites on HSA for $Hg^{2+}$ are likely to be the sulfur atoms of Cys-34. The secondary binding sites for $Hg^{2+}$ are represented by the sulfur from disulfide bridges, the negatively charged carboxylate oxygen, as well as the amide III nitrogen. The binding of $Hg^{2+}$ to HSA follows the first-order kinetics for mercurial species and zero-order kinetics for HAS (Yun et al. 2013). The characterization of mercury binding proteins in the human body is very important gain a deeper understanding of the metabolism and the mechanism of intoxication of ingested mercuric compounds.

Furthermore, recent findings deriving from animal models show how epidermal growth factor (EGF) administration

attenuates tubular necrosis following mercuric chloride damage; further studies are needed to confirm these preliminary findings (Yen et al. 2015), yet these findings may lay the foundation for a greater knowledge of how mercurial substances work and may allow the development of more effective treatments for mercurial intoxications.

### *Clinical features*

Mercuric chloride poses a risk through oral, dermal, and intravenous administration, while risk from inhalation is not described in the literature (ATSDR 1999). Mercuric chloride toxicity can present itself as acute, subacute, or chronic, depending on the nature and intensity of the exposure.

In mercuric chloride poisoning deaths, the oral route of administration, usually observed in suicides, is the most frequently reported in the literature (Gundrum 1913; Troen et al. 1951; Wands et al. 1974; Lino et al. 2009; Triunfante et al. 2009; Verma et al. 2010). Three cases of dermal administration, two of which were lethal, have been described (Millar 1916; Dyall-Smith and Scurry 1990; Kang-Yum and Oransky 1992). Only two cases of intravenous injection of mercuric chloride, depicting the almost simultaneous death of four individuals and the suicide of a drug-dependent man, respectively, have been reported in the literature (Harmon 1928).

The mean lethal dose of mercuric chloride is thought to be equal to 1–4 g, but there have been reports of adult fatalities after the ingestion of 0.5 g (Troen et al. 1951); thus, the severity of the poisoning is not as much dose-dependent as it would be expected. The extreme toxicity of this substance is exemplified by its $LD_{50}$, which is less than 3–6 mg/kg (Clarkson and Stockinger 1972). Because mercuric chloride can deposit itself in all tissues, the clinical manifestations of mercury toxicity involve multiple organs and apparatus with varying features and intensity.

The kidney appears to be the most vulnerable organ subjected to the toxicity of ingested mercuric chloride, as acute renal failure has been observed in a number of case studies of mercuric chloride ingestion (Afonso and De Alvarez 1960; Murphy et al. 1979; Samuels et al. 1982). Oliguria, proteinuria (increase in both albumin and β2-microglobulin), hematuria, nephritic syndrome, and granular casts have been reported (Afonso and De Alvarez 1960; Pesce et al. 1977). A case of rhabdomyolysis, with markedly elevated serum aldolase, lactate dehydrogenase, and creatinine phosphokinase, has been also reported (Chugh et al. 1978).

At the autopsy, pale and swollen kidneys have been observed (Murphy et al. 1979). Histological findings have confirmed the presence of tubular and glomerular pathology, as well as a severe proximal tubular atrophy and mercury deposition within the cortical interstitium and renal macrophages (Wands et al. 1974).

Limited information regarding respiratory effects after oral exposure to mercuric chloride has been reported so far. More specifically, the main findings were fine rales (Samuels et al. 1982), shortness of breath (Millar 1916), and a severe pulmonary edema that required artificial ventilation (Murphy et al. 1979).

Cardiovascular toxicity has been rarely observed following the ingestion of mercuric chloride. Tachycardia, as well as electrocardiographic changes consisting in the absence of the P wave, prolongation of the QRS segment, and a high T wave have been observed (Warkany and Hubbard 1953; Chugh et al. 1978). The clinical findings of mercury toxicity also include coronary heart disease, myocardial infarction, increases in carotid intimal medial thickness, carotid obstruction, and hypertension (Barr et al. 1972).

The only evidence of the hematological effects of mercury toxicity is the presence of anemia with thrombocytopenia (Murphy et al. 1979); in this case, the anemia is very likely secondary to the massive GI hemorrhage and to the metabolic acidosis that may develop with resultant circulatory compromise. Arterial blood gases should be monitored and any acid–base abnormalities managed supportively (Sabbe et al. 2008).

Concerning the GI effects, ingestion of mercuric chloride is recognized as an important irritating substance of the GI tract tissue. Blisters and ulcers of the mouth and throat (Chugh et al. 1978; Samuels et al. 1982), as well as vomiting, nausea, diarrhea, colicky abdominal pain, oropharyngeal pain, ulceration and hemorrhages throughout the length of the GI tract have been described (Millar 1916; Afonso and De Alvarez 1960; Murphy et al. 1979; Kang-Yum and Oransky 1992).

Little information regarding hepatic effects in mercuric chloride intoxication exists. The evidence of a jaundiced liver with elevated transaminase enzymes, alkaline phosphatase, lactate dehydrogenase, and bilirubin was reported; autopsy revealed an enlarged and softened liver (Murphy et al. 1979; Samuels et al. 1982).

As for the endocrine effects, up to now none have been reported after exposure to mercuric chloride.

With regard to the neurological effects, neurotoxicity has been observed even though mercuric chloride does not cross the blood–brain barrier efficiently. Among others, mild tremors, anxiety, depression, paranoid delusions, blurred vision, diplopia, and seizures have been reported (Barr et al. 1972). Autopsy findings have revealed abscesses in the occipital lobe and cerebellum (Murphy et al. 1979).

In relation to the reproductive system, mercuric chloride was used in an attempt to terminate pregnancy. Vaginal bleeding and uterine cramps, followed by the spontaneous abortion of the fetus and placenta, have been described (Afonso and De Alvarez 1960). At present, the possibility of transportation of mercury through the human placenta barrier has been postulated by many authors (Gundacker et al. 2010). Significantly higher mercury levels in the fetal blood compared to maternal blood have also been detected. An active placental transport to the fetus, probably through amino acid transporters, can thus be postulated (Stern and Smith 2003), but the exact mechanism remains largely unknown.

Only two cases of mercuric chloride intravenous administration have been described in the literature (Harmon 1928; Dittmann and Pribilla 1985). In one of them, the authors focus on comparing the effects between oral and intravenous administration, stating that liver damage, in the intravenous

administration, has consisted only in mild parenchymatous degeneration, in contrast to the severe hepatic changes observed after mercuric chloride poisoning taken orally. The renal changes have been found to be essentially the same whether the mercury was administered by mouth or by the intravenous route; no evidence of gastroenteritis has been observed at the autopsy after the intravenous injection.

## Diagnosis

### In vivo *and post-mortem mercury concentration*

The measurement of mercury serum concentrations is the most accurate means of diagnosing poisoning. Diagnosis of mercury overload is difficult, as the commonly used testing (blood, urine, and/or hair levels) do not correlate with the total body burden and offer little diagnostic useful information, while provocation with DMPS appears to offer a more sensitive assessment of body burden (Bernhoft 2012).

With regard to toxicological analyses, specimens should be collected as follows: blood, 10 mL, in K-EDTA tube; urine, 20 mL, in a sterile container or aliquot of a 24-h collection (Braithwaite 2011). Preservation of mercury in stored specimens requires acidification and freezing.

Urine is a good sample for assaying mercuric chloride. A concentration greater than 100 μg/L produces neurological signs, while a concentration greater than 800 μg/L is often associated with death (Rafati-Rahimzadeh et al. 2014).

Hair can also be useful in environmental studies or unusual clinical cases. Indeed, the hair is rich in sulfhydryl groups and mercury compounds show a high tendency to bind sulfur.

To date, we still lack a standard method to accurately assess mercury compounds content in the human body. Mercuric chloride is often determined in biological specimens using cold-vapor atomic absorption spectrometry (CV-AAS). This analytical procedure has been identified as the method of choice in the determination of mercuric chloride in a wide range of biological materials (Braithwaite 2011). Otherwise, inductively coupled plasma optical emission spectrometry (ICP OES) may be used as a screening technique for autopsy material in the case of acute poisoning by mercury, but not for hair or blood (Triunfante et al. 2009; Lech 2014).

Other techniques for determining mercury are available, including atomic absorption spectrometry with electrothermal atomization in a graphite furnace (GF AAS) (Gundacker et al. 2010), inductively coupled plasma mass spectrometry (ICP-MS) (Moreno et al. 2013; Li et al. 2014), X-ray fluorescence, and laser ablation inductively coupled plasma mass spectrometry (ICP-DRCMS) (Stadlbauer et al. 2005). Unfortunately, these techniques have not been reported in cases of mercuric chloride intoxication.

In lethal cases, mercuric chloride should be investigated in samples of blood, urine, hair and in specimens of organs; the analyses of these samples must be performed by taking into account of the normal and lethal ranges of mercury (Musshoff et al. 2004).

### *Other laboratory tests*

Initial general laboratory tests should include serum electrolytes, hemoglobin, blood urea nitrogen (BUN), creatinine, creatine kinase activity, albumin, serum aldolase, lactate dehydrogenase, and creatinine phosphokinase. Special care should be taken when interpreting hemogasanalysis for the risk of metabolic acidosis. A routine electrocardiogram and blood pressure measurement should also be performed to identify potential tachycardia and elevated blood pressure associated with mercuric chloride poisoning.

In addition to mercury assays, neuropsychiatric testing, nerve conduction studies, and urine assays for N-acetyl-β-D-glucosaminidase and $\beta_2$-microglobulin are recommended for the early detection of subclinical mercury toxicity. In summary, diagnosis is typically based on the individual's history and his/her clinical presentation.

### *Nano-technologies and their application in the diagnosis of mercury poisoning*

The use of nanotechnologies has revolutionized toxicological and medical sciences. Nanotechnologies have a broad range of applications, such as medical instruments and tools, drugs delivery and, in biomedical research, diagnosis, and treatment evaluation (Linkov et al. 2008; Surendiran et al. 2009). Effective methods, such as gold (AuNPs) and silver (AgNPs) nanoparticles, have been employed in studies regarding the diagnosis of mercury poisoning. AuNPs represent a rapid, inexpensive, and sensitive method for detecting RNA and DNA sequences (Baptista et al. 2008; Zuo et al. 2010). AgNPs, contained in antibacterial, sunscreens, and cosmetic agents, have been used as sensitive indicators of low concentrations of mercury in homogeneous aqueous solutions (Ahmed et al. 2014). This method has also been studied by Torabi and Lu (2011), who have designed a colorimetric sensor for mercury based on structure-switching DNA that contains mismatched thymine residues. The sensor has been designed for the immobilization of AuNP aggregates onto a lateral-flow device, resulting in an easy-to-use dipstick test for mercury capable of carrying out real-time mercury detection in environmental and medical applications.

Another method, reported for mercury removal using nanotechnologies (Zhang et al. 2019), is based on the use of $SnO_2$/aerogel, synthesized by a simple method form sodium alginate, which is characterized by high removal efficiency and large adsorption capacity, broad operating temperature windows, and resistance to high space velocity and $H_2O$. Even though these studies show promising results, they have to be confirmed by larger scale research.

## Management

### *Decontamination*

After the initial assessment and stabilization, the early management of an individual with mercuric chloride intoxication includes: (a) GI decontamination; (b) washing of exposed skin (if dermal contact has occurred); (c) supportive measures, such as hydration, supplemental oxygen, endotracheal

intubation, and mechanical ventilation; (d) baseline diagnostic studies, such as complete blood count, serum chemistries, arterial blood gas, radiographs, and electrocardiogram; (e) specific analyses of blood and urine to detect mercury; (f) contemplation of possible co-intoxicants; (g) and careful monitoring (Rafati-Rahimzadeh et al. 2014).

From a clinical point of view, the ingestion of mercuric chloride may lead to cardiovascular collapse caused by severe gastroenteritis and third-space fluid loss, therefore fluid resuscitation is a priority.

GI decontamination should be implemented for mercuric chloride intoxication because of systemic absorption, but the corrosive property of this substance represents an important limitation. In spite of the corrosiveness of mercuric chloride and the potential risk for perforation, the removal from absorptive surfaces should take priority over endoscopic evaluation.

Moreover, in the majority of cases, the prominence of vomiting makes gastric lavage unnecessary for most individuals with mercuric chloride poisoning.

Whole-bowel irrigation with polyethylene glycol solution may be useful to remove residual mercury. In this case, serial abdominal radiographies are needed for patient follow-up (Young-Jin 2011). Activated charcoal may be used for the treatment of mercuric chloride intoxication, but its efficacy is still controversial. Indeed, while having limited binding capacity for metallic compounds in general, there is *in vitro* evidence for adsorption of mercuric chloride, but charcoal could obscure visibility if endoscopy is required (Beasley et al. 2014).

### *Supportive care*

The major complications of mercuric chloride poisoning are renal failure, GI symptoms, and cardiovascular collapse, thus close monitoring for renal, GI, cardiovascular, and respiratory functions is mandatory. Stabilization consists in an appropriate airway management, securing intravenous access, often followed by inotropic and/or vasopressor agents administration, intravenous fluids administration, and a close cardiac and renal monitoring.

GI blood losses may be sufficient to produce anemia, requiring transfusion. In individuals with severe gastric necrosis, surgical intervention may be required (Murphy et al. 1979). Caustic injury to the oropharyngeal mucosa may produce edema and subsequent obstruction requiring airway protection, ventilatory support, and tracheostomy. Metabolic acidosis may develop with resultant circulatory collapse (Sabbe et al. 2008). For this reason, arterial blood gases should be monitored, and any acid–base abnormalities managed supportively. Finally, individuals at risk of rhabdomyolysis should have their creatine kinase activity and serum or urine myoglobin concentrations measured.

### *Chelation therapy*

After initial medical stabilization and decontamination, early institution of chelators may minimize or prevent the widespread effects of poisoning. The studies carried out in the late 1940s have laid the foundation for the modern therapy with chelating agents such as dimercaprol (BAL), 2,3-dimercaptosuccinic acid (succimer), and 2,3-dimercapto-1-propanesulphonate (DMPS) (McGown et al. 1984; Vilensky and Redman 2003). These treatments are the most successful in removing the mercuric chloride from the organism.

Chelators have thiol groups that compete with endogenous sulfhydryl groups for the binding of mercury, thereby preventing inactivation of sulfhydryl-containing enzymes and other essential proteins. Furthermore, a high degree of protein binding and distribution to the brain is considered responsible for the lack of efficacy of other measures to increase mercury clearance, such as peritoneal dialysis and hemodialysis (Sauder et al. 1988).

In conclusion, decisions on chelation therapy should be made as early as possible, since experimental evidence has suggested that when chelation is delayed its efficacy can be diminished (Kosnett 2010).

### *Dimercaprol or British anti-Lewisite (BAL)*

BAL (2,3-dimercaptopropanol) is a metal chelator used clinically for heavy metal toxicity. The role of BAL in mercury poisoning is being superseded by succimer and 2,3-dimercapto-1-propane sulfonic acid (DMPS), unless the GI tract is affected and BAL is indicated. No recent pharmacokinetic studies on BAL have been published and the only information available in the literature dates back to the late 1940s (Longcope and Luetscher 1949). Few data concerning the toxicity of BAL exist; dose-dependent effects and affection by urinary pH have been demonstrated. BAL should not be administered at doses greater than 5 mg/kg because of the high risk of adverse reactions. Concerning therapeutic dosages, no clinical trial has ever attempted to identify the best dose of BAL. BAL administration in decreasing doses for ten days is considered the main treatment for clinically significant acute poisoning due to inorganic mercury, such as mercuric chloride, in the US.

BAL should only be administered through deep intramuscular injection, since unintentional intravenous infusion could produce important life-threatening events such as fat embolism, lipoid pneumonia, chylothorax, and associated hypoxia (Howland 2011). When BAL is administered at high doses, the following symptoms have been reported: agitation, anxiety, chest pain, diaphoresis, tooth pain, burning and tingling of extremities, muscle aches, increased salivation, rhinorrhea, lacrimation, burning sensation of lips, mouth, throat, and eyes, headache, vomiting, nausea, elevations in systolic and diastolic blood pressure, tachycardia, fever, and transient reduction in the percentage of polymorphonuclear leukocytes (Howland 2011).

### *2,3-dimercaptosuccinic acid (succimer, DMSA)*

Succimer is a protein highly bound to albumin through a disulfide bond, which enhances the elimination of mercury. It has been widely used to treat individuals with mercuric chloride intoxication as well as those with other heavy metal poisonings (Bradberry and Vale 2009a, 2009b).

The metabolism of succimer has been investigated extensively in animal studies through intravenous and oral radio-

labeled administration. Following an intravenous dose, the substance is eliminated almost exclusively via the kidney, with only trace amounts (less than 1%) excreted *via* the feces or expired air (McGown et al. 1984). Succimer improves survival, decreases renal damage, and enhances elimination of mercury in animals following exposure to mercuric chloride (Magos 1976; Buchet and Lauwerys 1989). However, a study in mice who were subjected to intraperitoneal mercuric chloride has demonstrated an enhanced deposition of mercury in motor neurons following chelation with succimer or DMPS (Ewan and Pamphlett 1996).

The use of succimer in pregnancy is controversial and usually contraindicated. In animal studies, it has been shown a dose-dependent effect of succimer on early and late fetal resorption, as well as on fetal body weight and length. Doses of 410–1640 mg/kg/day of succimer, administered subcutaneously to pregnant mice during organogenesis, have been demonstrated to be teratogenic and fetotoxic (Magos 1988).

Human studies, conducted on both children and adults, have shown that succimer undergoes an enterohepatic circulation facilitated by the GI microbiota (Asiedu et al. 1995).

Few adverse events related to the administration of succimer have been reported. These are represented by nausea, vomiting, flatus, diarrhea, chills, fever, urticaria, rash, reversible neutropenia, eosinophilia and, less frequently, a metallic taste. Mild elevations in transaminase enzymes have also been reported (Howland 2011). A single case of severe hyperthermia and hypotension, related to succimer administration, has been reported (Okose et al. 1991). Concerning the safety of succimer, few clinical trials have been carried out, leading to limited knowledge on this topic. Because of the several adverse effects that may result from BAL chelation therapy, oral succimer is recommended in individuals who are not acutely ill or who have been chronically poisoned.

The succimer dosage differs between children and adults. At approximately 5 years of age, dosing based on body surface area approximates the dose for adults (10 mg/kg), while for children less than 5 years of age dosing by body surface area gives higher doses and is recommended. The suggested dosage for children is 350 mg/m$^2$, three times a day for five days, followed by 350 mg/m$^2$ twice a day for 14 d. In adults, the dosage is 10 mg/kg three times a day for five days followed by 10 mg/kg twice a day for 14 d (Howland 2011).

Recent studies have shown that esters of succimer may be more effective antidotes for heavy metal poisoning. These compounds are mono- and di-esters of succimer that can enhance tissue elimination of mercury. New and experimental therapies for mercury chelation, using DMSA analogous such as monoisoamyl ester of DMSA (MiADMSA), monomethyl DMSA (MmDMSA), and monocyclohexyl DMSA (MchDMSA), have been carried out (Flora and Pachauri 2010). In spite of the encouraging results, larger scale research is required to evaluate the efficacy of these substances.

### *2,3-dimercapto-1-propane sulfonic acid (DMPS)*

DMPS, similarly to succimer, is a water-soluble analog of BAL (Campbell et al. 1986). A dose of 15 mg/kg of DMPS is equimolar to 12 mg/kg of succimer. The role of DMPS in mercuric chloride intoxication has been widely studied in animal models. These studies have mainly focused on the reduction of brain mercury concentration following the administration of mercuric chloride. The administration of oral DMPS in mice given mercuric chloride orally has reduced brain mercury concentrations significantly ($p<.05$), to less than 21% of that in controls (Nielsen and Andersen 1991). The role of DMPS in mice treated with intravenous injection of mercuric chloride has also been studied by Aaseth, who demonstrated an important reduction of brain mercury concentrations to approximately 38% (Aaseth 1983). Similarly, brain mercury concentrations were reduced, but not significantly so, by intraperitoneal DMPS administration in mice treated with mercuric chloride (Planas-Bohne 1981).

In human, DMPS therapy has been found to produce a marked increase in $Zn^{2+}$ and $Cu^{2+}$ excretion. Nevertheless, this increase did not result in clinically significant complications (Bradberry et al. 2009). Torres-Alanis et al. previously reported similar increases in $Zn^{2+}$, $Cu^{2+}$, and $Mg^{2+}$ excretion after a single dose of DMPS (Torres-Alanis et al. 2000). The increase in $Cu^{2+}$ excretion, in individuals to whom DMPS was administered, has been associated with a major frequency of Stevens-Johnson syndrome (Van der Linde et al. 2008).

Differences in the chelation protocols between the US and Europe exists. BAL and the succimer are considered the treatment of choice in poisoning due to inorganic mercury, such as mercuric chloride, in the US. In Europe, DMPS represents the most important drug administered in such a condition and it may be administered both intravenously and orally.

Decisions on chelation should be made early as experimental evidence has suggested that when chelation is delayed its efficacy may diminish (Kosnett 2010).

### *Plasma exchange-hemodialysis-plasmapheresis*

Plasma exchange is, usually, the first and urgent approach to poisoning when the individual's life is in danger and there is no suitable alternative therapy. This treatment can be used until about 24–36 h after the clinical diagnosis.

Hemodialysis represents the best approach for water-soluble and dialyzable substances and it may be necessary if renal failure occurs (Dargan et al. 2003). At times, toxic substances can strongly bind to plasma proteins and cannot be removed by hemodialysis; in such cases, plasmapheresis could be a useful alternative to remove protein-bound heavy metals in plasma, such as mercury. Some toxicologists suggest performing these procedures in combination with chelating agents. Indeed, in mono-therapy the elimination half-life of mercuric chloride may vary from 30 to 100 d. When DMPS and hemodialysis are co-administered, the elimination half-life may be decreased to about 2–8 d (Nenov et al. 2003). Finally, hemodialysis may be ultimately necessary because of the acute renal failure that frequently occurs after mercuric chloride poisoning.

## Conclusions

A review about the mechanisms of toxicity, the clinical symptoms, the medical treatments, the *post-mortem* findings, and

the analytical procedures concerning mercuric chloride intoxication is here presented. The knowledge of all the cases of mercuric chloride toxicity described in the literature over the years and how these have been managed is of great importance as it represents a useful starting point for a better understanding of this kind of poisoning. Indeed, mercury exposure should be considered a silent threat to environment and human life, and mercuric chloride intoxications are, still nowadays, encountered in our emergency departments and morgues, representing a great challenge for all the specialists involved, including the forensic toxicologists and pathologists.

In the majority of cases, deaths are caused by the accidental administration of the compound, even though cases of suicidal or homicidal administrations are reported in the medical literature. The primary toxicity and the *post-mortem* findings observed when mercuric chloride is involved are similar to those of other heavy metals and are a combination of renal damage leading to renal failure and anuria, lesions of the GI tract, cardiovascular collapse, CNS symptoms, and death.

There is no specific management for individuals with mercuric chloride-related toxicity; it is essential that the renal function and the volemic status are preserved with the use of chelating agents and supportive care medications as rapidly as possible to try and reduce the systemic toxicity and prevent the possible subsequent death.

New protocols for the treatment of poisoning such as access to nanotechnologies (e.g. specific nanosorbents), chelating agents, and combination therapies can help in the management of mercuric chloride intoxication. Otherwise, familiarity with the current therapy protocols is a necessary requirement, especially when the forensic pathologist is asked by the Prosecutor's Office to evaluate the appropriateness of the treatment and the medical responsibility.

In lethal cases, the *post-mortem* findings that should lead the forensic pathologist to suspect mercuric chloride poisoning derive from the autopsy examination and from a negative standard toxicological screening. In these cases, the site survey, as well as the collection of circumstantial information, items, chemicals, and drugs from the crime scene are of fundamental importance. The competence and the appropriate skills of the forensic pathologist are needed not only to conduct an accurate autoptic examination, but also to guide the forensic toxicologist in the research of those substances that are not routinely analyzed.

In conclusion, it is important to be aware of the potential toxicity of mercuric chloride. Based on this review of the literature, we strongly recommend a close observation and an aggressive supportive care, along with early chelation, preferably with succimer or DMPS, for the treatment of this potentially life-threatening poisoning.

## Acknowledgments

Technical assistance from Dr. Santina Cantatore of the University of Foggia is gratefully acknowledged. We thank Dr. Alessandro Santurro and Matteo Scopetti of the Sapienza University of Roma for taking the time for providing supplementary data from recent studies. These comments were very useful in revising this article.

## Declaration of interest

In accordance with Taylor and Francis policy and ethical obligations, the authors declare to have no conflict of interest. No funding was received for this project. The regular employment affiliation of the authors is shown on the cover page. This critical review was conducted during the normal course of the authors'employment using institutional funding. No outside funds were used to prepare the review. The preparation of the review, conclusions drawn, and the recommendations made are the exclusive professional work product of the authors and may not necessarily be those of the employers. None of the authors has participated in regulatory or legal proceeding during the past five years related to the contents of this article.

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