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Is calomel truly a poison and what happens when it enters the human stomach? A study from the thermodynamic viewpoint

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Abstract: The chemical and electrochemical equilibria involving mercurous and mercuric chlorides in the conditions, corresponding to the human stomach environment, were studied from the point of view of chemical thermodynamics. The Gibbs free energies of formation of various mercury and chlorine compounds, the equilibrium constants, and the electrode potentials of reactions involving these compounds at 37°C were calculated. The potential-pH diagrams of Hg_2^{2+}-H_2O, Cl^--H_2O, and Hg_2^{2+}-Cl^--H_2O systems were plotted. The question of how toxic is calomel when ingested was discussed.

Keywords: calomel; human stomach; mercury chlorides; Pourbaix diagram; toxicity.

Introduction

In his recent paper titled 'Mercury(I) Chloride *In Vivo* Oxidation: A Thermodynamic Study', Mousavi (2015) discussed the medical usage and the toxicity of mercurous and mercuric chlorides. He raised the hypothesis that when calomel enters the stomach, it will almost entirely be converted to $HgCl_2$. Then he presented the thermodynamic calculations that, in the author's opinion, 'prove' this hypothesis and assumed that Napoleon's death could had been caused by administering calomel into his body. Later he published another paper (Burke et al., 2015), in which he assumed the responsibility of calomel ingestion for another historical death.

Unfortunately, the thermodynamic calculations performed by Mousavi (2015) are very tenuous, and his conclusions are crude and premature. In fact, he only calculated the equilibrium constant for the reaction $2Hg_2^{2+}(aq)+4H^+(aq)+O_2(g)\rightarrow 4Hg^{2+}(aq)+2H_2O(l)$ at 37°C using the van't Hoff isochore equation (van't Hoff, 1884), observed that it has the order of magnitude of 10^{19}, and concluded that calomel in the human stomach would be completely converted to $HgCl_2$. However, such hypotheses cannot be based only on the analysis of a single reaction. At least the possible side reactions and the alternative products of mercury (I) oxidation should be taken into consideration. The influence of concentration of the species on equilibrium conditions should not be disregarded. Therefore, this study aims to perform the more rigorous thermodynamic analysis of mercury (I) oxidation in human stomach and to extend the approach given by Mousavi (2015).

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Results and discussion

Thermodynamic data on aqueous mercury and chlorine compounds

Mercury in an aqueous environment can form the following species: Hg (aq), Hg_2^{2+} (aq), Hg^{2+} (aq), $HgOH^+$ (aq), $Hg(OH)_2$ (aq), and $Hg(OH)_3^-$ (aq). The aqueous species of chlorine are the following: Cl^- (aq), HCl (aq), Cl_2 (aq), ClO^- (aq), HClO (aq), ClO_2^- (aq), $HClO_2$ (aq), ClO_2 (aq), ClO_3^- (aq), $HClO_3$ (aq), ClO_4^- (aq), and $HClO_4$ (aq). Mercury (II) can form not only the chloride $HgCl_2$ (aq) but also the cation $HgCl^+$ (aq) and the anions $HgCl_3^-$ (aq) and $HgCl_4^{2-}$ (aq). In addition, the solid Hg_2Cl_2 and HgO; the liquid Hg and H_2O; the gaseous H_2, O_2, and Cl_2; and the aqueous H^+ and OH^- can be present in the system (Schweitzer and Pesterfield, 2010).

The average temperature inside the stomach is equal to the human core body temperature of 37.6°C (Cagnacci et al., 1997; Houdas and Ring, 2013). The gastric fluid consists primarily of HCl (Prout, 1824; Davies, 1951), which average concentration is about 0.5% or 0.14 mol L^{-1} (MacLean and Griffiths, 1928; Ash, 2011). Sodium and potassium chlorides are also present in the gastric fluid (Hollander, 1952; Torosov, 1966), which raises the average

concentration of chloride ions in the stomach up to 0.2 mol L^{-1} (Lee et al., 1955; Strong et al., 1960; Mößeler et al., 2010). The gastric gas present in the stomach includes up to 16% of oxygen (Dunn and Thompson, 1923; Forth and Adam, 2001; Kanner and Lapidot, 2001) and no more than $3 \cdot 10^{-6}$% of hydrogen (Borgeskov et al., 1966; Urita et al., 2006).

The standard Gibbs energies and the standard enthalpies of formation of the aforementioned mercury and chlorine compounds were collected from various sources (Wagman et al., 1982; Bard et al., 1985; Chase et al., 1998; Speight, 2005; Schweitzer and Pesterfield, 2010). Because the difference between the human core body temperature (310.75 K) and the reference temperature (298.15 K) is small, the enthalpies and entropies of formation may be treated as constant and independent of temperature, and the Gibbs energies of formation of compounds may be calculated according to the Helmholtz-Gibbs equation (Helmholtz, 1882, 1883) as follows:

$$\Delta_f G_{310.75} = \Delta_f H_{298.15} - 310.75 \cdot \Delta_f S_{298.15} = \Delta_f H_{298.15} - 310.75 \cdot \frac{\Delta_f H_{298.15} - \Delta_f G_{298.15}}{298.15}. \quad (1)$$

The calculated values of $\Delta_f G_{310.75}$ are listed in Table 1.

The ionic strength of the intestinal solution is determined by the concentration of the chlorides, and the assumption was made that it is equal to 0.2 mol L^{-1}. The activity coefficient of the chloride ion was calculated according to the extended Debye-Hückel equation (Debye and Hückel, 1923). The values of the effective radii of the ions were taken from the paper of Kielland (1937), and the value of dielectric constant of water at 310.75 K needed for calculation of the parameters in Debye-Hückel equation was collected from the papers of Coolidge (1899), Wyman (1930), and Malmberg and Maryott (1956). The calculated value of the activity coefficient equals 0.610, leading to $a_{Cl^-(aq)} = 0.122$ mol L^{-1}. The concentration of mercurous ions in the stomach is determined by the maximum solubility of solid calomel at 310.75 K and equals $1.2 \cdot 10^{-6}$ mol L^{-1}. At such low concentrations, the solution can be treated as the ideal one, and the activity is assumed equal to concentration. Because the concentrations of the other mercury and chlorine ions that can be formed from Hg_2^{2+} (produced by calomel) and Cl^- (from the gastric fluid) cannot exceed the concentrations of these two ions, the assumption was made and used in further calculations that the activities of all chlorine ions are equal to 0.1 mol L^{-1}, and the activities of all mercury ions except those containing both mercury and chlorine are equal to 10^{-6} mol L^{-1}. Liquid mercury is a pure substance, and its activity is equal to unity.

Table 1: The Gibbs energies of formation of compounds in Hg_2^{2+}-Cl^--H_2O system at 310.75 K and 1 bar.

Compound	$\Delta_f G_{310.75}$ (J mol^{-1})	Compound	$\Delta_f G_{310.75}$ (J mol^{-1})
Hg (l)	0	Cl_2 (g)	0
Hg (aq)	39370	Cl_2 (aq)	8220
Hg^{2+} (aq)	164120	ClO^- (aq)	42880
Hg_2^{2+} (aq)	152720	ClO_2 (aq)	122010
HgO (s)	-57050	ClO_2^- (aq)	20740
$HgOH^+$ (aq)	-50940	ClO_3^- (aq)	-3890
$Hg(OH)_2$ (aq)	-271400	ClO_4^- (aq)	-3410
$Hg(OH)_3^-$ (aq)	-427200	HCl (aq)	-129710
$HgCl^+$ (aq)	-4830	HClO (aq)	-78170
$HgCl_2$ (aq)	-171380	$HClO_2$ (aq)	8340
$HgCl_3^-$ (aq)	-305740	O_2 (g)	0
$HgCl_4^{2-}$ (aq)	-442270	H_2 (g)	0
Hg_2Cl_2 (s)	-208440	OH^- (aq)	-154150
Cl^- (aq)	-129710	H_2O (l)	-235070

Equilibria involving mercuric and chloride ions

The interaction of Hg^{2+} with Cl^- may result in the following reactions:

$$Hg^{2+}(aq) + Cl^-(aq) \rightleftharpoons HgCl^+(aq), \quad (2)$$

$$HgCl^+(aq) + Cl^-(aq) \rightleftharpoons HgCl_2(aq), \quad (3)$$

$$HgCl_2(aq) + Cl^-(aq) \rightleftharpoons HgCl_3^-(aq), \quad (4)$$

$$HgCl_3^-(aq) + Cl^-(aq) \rightleftharpoons HgCl_4^{2-}(aq). \quad (5)$$

The values of equilibrium constants of Equations 2–5 at 310.75 K were calculated from the values of the Gibbs energies of formation of compounds using the van't Hoff isotherm equation (van't Hoff, 1884). The following values were obtained: $K_{(2)} = 3944847$ L mol^{-1}, $K_{(3)} = 1554731$ L mol^{-1}, $K_{(4)} = 6.0433$ L mol^{-1}, and $K_{(5)} = 14.0301$ L mol^{-1}. The values of the thermodynamic activities of the ions are related to one another with the expressions of equilibrium constants and the equation of the material balance as follows:

$$\frac{a_{HgCl^+(aq)}}{a_{Hg^{2+}(aq)} \cdot a_{Cl^-(aq)}} = 3944847 \text{ mol } L^{-1}, \quad (6)$$

$$\frac{a_{HgCl_2(aq)}}{a_{HgCl^+(aq)} \cdot a_{Cl^-(aq)}} = 1554731 \text{ mol } L^{-1}, \quad (7)$$

$$\frac{a_{HgCl_3^-(aq)}}{a_{HgCl_2(aq)} \cdot a_{Cl^-(aq)}} = 6.0433 \text{ mol L}^{-1}, \quad (8)$$

$$\frac{a_{HgCl_4^{2-}(aq)}}{a_{HgCl_3^-(aq)} \cdot a_{Cl^-(aq)}} = 14.0301 \text{ mol L}^{-1}, \quad (9)$$

$$a_{Hg^{2+}(aq)} + a_{HgCl^+(aq)} + a_{HgCl_2(aq)} + a_{HgCl_3^-(aq)} + a_{HgCl_4^{2-}(aq)} = 10^{-6} \text{ L mol}^{-1}. \quad (10)$$

After substituting the condition $a_{Cl^-}=0.1$ mol L^{-1} into Equations 6–10, they transfer to the system of five equations with five variables, which have the following unambiguous solution: $a_{Hg^{2+}(aq)}=6.649\cdot10^{-18}$ mol L^{-1}, $a_{HgCl^+(aq)}=2.623\cdot10^{-12}$ mol L^{-1}, $a_{HgCl_2(aq)}=4.078\cdot10^{-7}$ mol L^{-1}, $a_{HgCl_3^-(aq)}=2.464\cdot10^{-7}$ mol L^{-1}, and $a_{HgCl_4^{2-}(aq)}=3.458\cdot10^{-7}$ mol L^{-1}.

When the mercuric and the chloride ions coexist in a solution, the predominant forms of their existence are neutral $HgCl_2$ and the anions $HgCl_3^-$ and $HgCl_4^{2-}$ with approximately equal ratio between them. The cationic forms Hg^{2+} and $HgCl^+$ exist in a much smaller degree.

Equilibria in Hg_2^{2+}-H_2O and Cl^--H_2O systems

The most compact way of presentation of the chemical and electrochemical equilibria in the aqueous redox systems is the potential-pH diagram, initially proposed by Pourbaix (1945, 1963) and Delahay et al. (1950). The procedure of constructing the Pourbaix diagrams was described in detail several times; the most recent description was made by Schweitzer and Pesterfield (2010). The equations of electrochemical equilibria can be calculated using the Nernst equation (Nernst, 1887, 1889), and the expression similar to Henderson-Hasselbalch equation (Henderson, 1908; Hasselbalch, 1917) is used for calculating pH (Sørensen, 1909a,b) of chemical equilibria. The values of the Gibbs energies of formation of compounds from Table 1 were used in calculations.

The potential-pH diagram of Hg_2^{2+}-H_2O system at 310.75 K, 1 bar, and $a_{[Hg]\,(aq)}=10^{-6}$ mol L^{-1} is presented in Figure 1, and the potential-pH diagram of Cl^--H_2O system at 310.75 K, 1 bar, and $a_{[Cl]\,(aq)}=0.1$ mol L^{-1} is presented in Figure 2. The calculated characteristics of the chemical and electrochemical equilibria are listed in Table 2.

The Pourbaix diagram for mercury shows that it can form both mercurous and mercuric cations or be oxidized to aqueous $Hg(OH)_2$ or $Hg(OH)_3^-$, whereas aqueous $HgOH^+$ and solid HgO are thermodynamically unstable. The diagram for chlorine indicates that the only stable forms

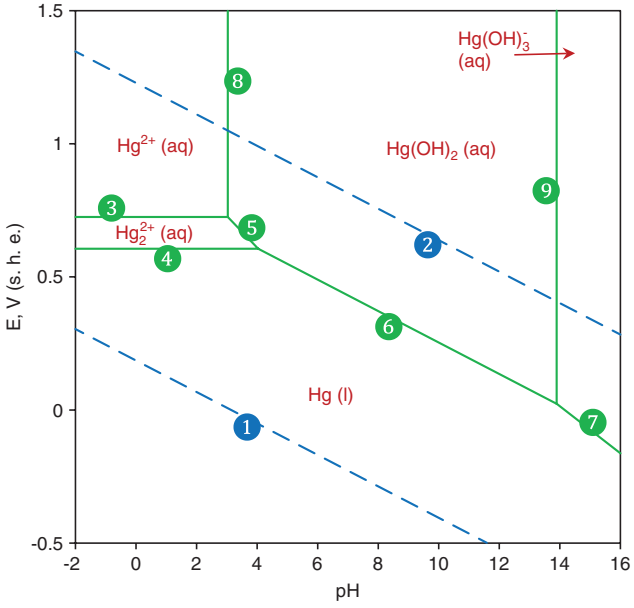

Figure 1: The potential-pH diagram of Hg_2^{2+}-H_2O system at 310.75 K and 1 bar.

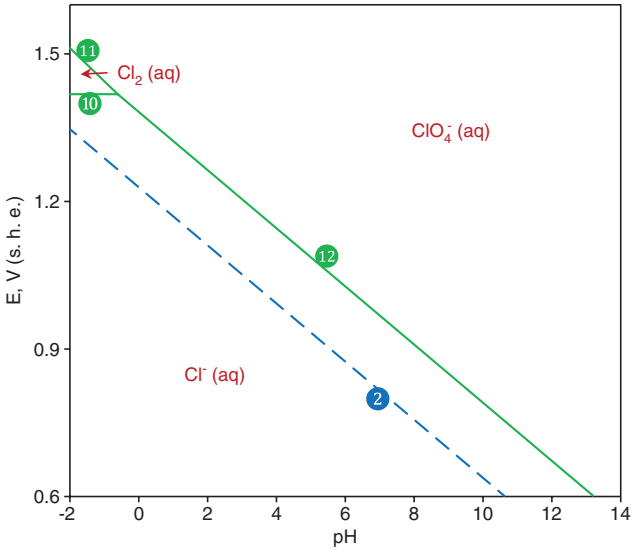

Figure 2: The potential-pH diagram of Cl^--H_2O system at 310.75 K and 1 bar.

of chlorine in solution are the chloride and the perchlorate ion and the aqueous elemental chlorine.

Equilibria in Hg_2^{2+}-Cl^--H_2O system

The method of constructing the potential-pH diagrams of the multielement systems is described by Thompson et al. (2011). The diagram of Hg_2^{2+}-Cl^--H_2O system was

Table 2: The thermodynamic characteristics of basic chemical and electrochemical equilibria in Hg_2^{2+}-H_2O, Cl^--H_2O, and Hg_2^{2+}-Cl^--H_2O systems at 310.75 K and 1 bar.

Line at figures 1–3	Equilibrium reaction	Activities (a, mol L^{-1}) or partial pressures (p, bar) of the components	E, V (s. h. e.), or pH of the solution
1	$2H^+(aq)+2e^- \rightleftharpoons H_2(g)$	$p_{H_2(g)}=3\cdot10^{-6}$	$E=0.170-0.0309\cdot pH$
2	$O_2(g)+4H^+(aq)+4e^- \rightleftharpoons 2H_2O(l)$	$p_{O_2(g)}=0.16$; $a_{H_2O(l)}=1$	$E=1.206-0.0309\cdot pH$
3	$2Hg^{2+}(aq)+2e^- \rightleftharpoons Hg_2^{2+}(aq)$	$a_{Hg^{2+}(aq)}=10^{-6}$; $a_{Hg_2^{2+}(aq)}=10^{-6}$	$E=0.725$
4	$Hg_2^{2+}(aq)+2e^- \rightleftharpoons 2Hg(l)$	$a_{Hg_2^{2+}(aq)}=10^{-6}$; $a_{Hg(l)}=1$	$E=0.606$
5	$2Hg(OH)_2(aq)+4H^+(aq)+2e^- \rightleftharpoons Hg_2^{2+}(aq)+4H_2O(l)$	$a_{Hg(OH)_2(aq)}=10^{-6}$; $a_{Hg_2^{2+}(aq)}=10^{-6}$; $a_{H_2O(l)}=1$	$E=1.083-0.1234\cdot pH$
6	$Hg(OH)_2(aq)+2H^+(aq)+2e^- \rightleftharpoons Hg(l)+2H_2O(l)$	$a_{Hg(OH)_2(aq)}=10^{-6}$; $a_{Hg(l)}=1$; $a_{H_2O(l)}=1$	$E=0.845-0.0617\cdot pH$
7	$Hg(OH)_3^-(aq)+3H^+(aq)+2e^- \rightleftharpoons Hg(l)+3H_2O(l)$	$a_{Hg(OH)_3^-(aq)}=10^{-6}$; $a_{Hg(l)}=1$; $a_{H_2O(l)}=1$	$E=1.256-0.0926\cdot pH$
8	$Hg(OH)_2(aq)+2H^+(aq) \rightleftharpoons Hg^{2+}(aq)+2H_2O(l)$	$a_{Hg(OH)_2(aq)}=10^{-6}$; $a_{Hg^{2+}(aq)}=10^{-6}$; $a_{H_2O(l)}=1$	$pH=2.909$
9	$Hg(OH)_3^-(aq)+H^+(aq) \rightleftharpoons Hg(OH)_2(aq)+H_2O(l)$	$a_{Hg(OH)_3^-(aq)}=10^{-6}$; $a_{Hg(OH)_2(aq)}=10^{-6}$; $a_{H_2O(l)}=1$	$pH=13.320$
10	$Cl_2(aq)+2e^- \rightleftharpoons 2Cl^-(aq)$	$a_{Cl_2(aq)}=0.1$; $a_{Cl^-(aq)}=0.1$	$E=1.418$
11	$2ClO_4^-(aq)+16H^+(aq)+14e^- \rightleftharpoons Cl_2(aq)+8H_2O(l)$	$a_{ClO_4^-(aq)}=0.1$; $a_{Cl_2(aq)}=0.1$; $a_{H_2O(l)}=1$	$E=1.377-0.0705\cdot pH$
12	$ClO_4^-(aq)+8H^+(aq)+8e^- \rightleftharpoons Cl^-(aq)+4H_2O(l)$	$a_{ClO_4^-(aq)}=0.1$; $a_{Cl^-(aq)}=0.1$; $a_{H_2O(l)}=1$	$E=1.382-0.0617\cdot pH$
13	$Hg^{2+}(aq)+2e^- \rightleftharpoons Hg(l)$ $HgCl^+(aq)+2e^- \rightleftharpoons Hg(l)+Cl^-(aq)$ $HgCl_2(aq)+2e^- \rightleftharpoons Hg(l)+2Cl^-(aq)$ $HgCl_3^-(aq)+2e^- \rightleftharpoons Hg(l)+3Cl^-(aq)$ $HgCl_4^{2-}(aq)+2e^- \rightleftharpoons Hg(l)+4Cl^-(aq)$	$a_{Hg^{2+}(aq)}=6.649\cdot10^{-18}$; $a_{HgCl^+(aq)}=2.623\cdot10^{-12}$; $a_{HgCl_2(aq)}=4.078\cdot10^{-7}$; $a_{HgCl_3^-(aq)}=2.464\cdot10^{-7}$; $a_{HgCl_4^{2-}(aq)}=3.458\cdot10^{-7}$; $a_{Cl^-(aq)}=0.1$; $a_{Hg(l)}=1$	$E=0.321$
14	$Hg(OH)_2(aq)+2H^+(aq) \rightleftharpoons Hg^{2+}(aq)+2H_2O(l)$ $Hg(OH)_2(aq)+2H^+(aq)+Cl^-(aq) \rightleftharpoons HgCl^+(aq)+2H_2O(l)$ $Hg(OH)_2(aq)+2H^+(aq)+2Cl^-(aq) \rightleftharpoons HgCl_2(aq)+2H_2O(l)$ $Hg(OH)_2(aq)+2H^+(aq)+3Cl^-(aq) \rightleftharpoons HgCl_3^-(aq)+2H_2O(l)$ $Hg(OH)_2(aq)+2H^+(aq)+4Cl^-(aq) \rightleftharpoons HgCl_4^{2-}(aq)+2H_2O(l)$	$a_{Hg^{2+}(aq)}=6.649\cdot10^{-18}$; $a_{HgCl^+(aq)}=2.623\cdot10^{-12}$; $a_{HgCl_2(aq)}=4.078\cdot10^{-7}$; $a_{HgCl_3^-(aq)}=2.464\cdot10^{-7}$; $a_{HgCl_4^{2-}(aq)}=3.458\cdot10^{-7}$; $a_{Cl^-(aq)}=0.1$; $a_{Hg(OH)_2(aq)}=10^{-6}$; $a_{H_2O(l)}=1$	$pH=8.496$

constructed using the diagrams of Hg_2^{2+}-H_2O and Cl^--H_2O systems and the data on the equilibria in Hg^{2+}-Cl^- system and presented in Figure 3. The calculated characteristics of the chemical and electrochemical equilibria are listed in Table 2. The diagram shows that both the solid Hg_2Cl_2 and the aqueous Hg_2^{2+} have no domains of thermodynamic stability in the presence of the chloride ions.

The dashed lines in Figures 1–3, described by Equations 1 and 2 in Table 2, represent the equilibria corresponding to the hydrogen and the oxygen electrodes in the human stomach environment. The domain between these lines corresponds to the area of the electrochemical stability of water.

Conclusion

The acidity in a human stomach varies from pH 1 to 5, depending on time of a day and the condition of the digestive tract (Kong and Singh, 2008a,b, 2009; Beasley et al., 2015). This variety of environments is depicted in Figure 3 as the hatched area. As can be seen, either the mixture of Hg^{2+} (aq), $HgCl^+$ (aq), $HgCl_2$ (aq), $HgCl_3^-$(aq), and $HgCl_4^{2-}$(aq) or the liquid mercury is thermodynamically stable in the gastric fluid environment, depending on the equilibrium potential in the system. Therefore, the hypothesis raised by Mousavi (2015) is only a partial case. When the solid calomel enters the stomach, it will be oxidized

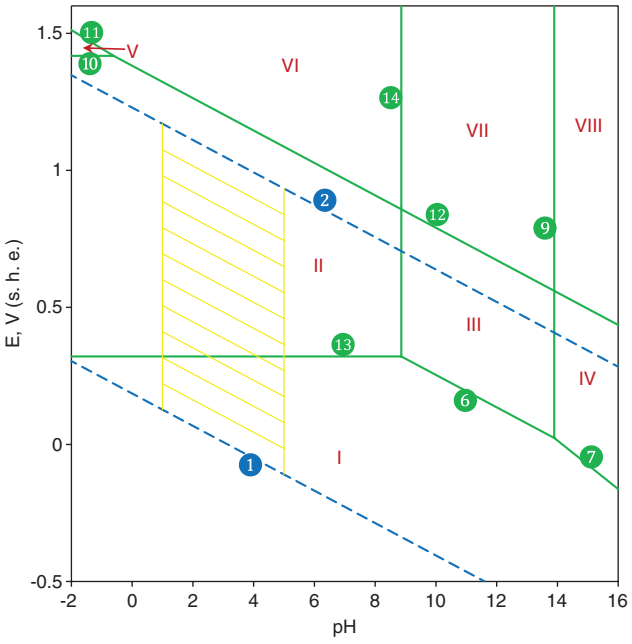

Figure 3: The potential-pH diagram of Hg_2^{2+}-Cl^--H_2O system at 310.75 K and 1 bar.
The domains of thermodynamic stability: I-Hg (l)+Cl^- (aq); II-Hg^{2+} (aq), $HgCl^+$ (aq), $HgCl_2$ (aq), $HgCl_3^-$ (aq), $HgCl_4^{2-}$ (aq), Cl^- (aq); III-$Hg(OH)_2$ (aq), Cl^- (aq); IV-$Hg(OH)_3^-$ (aq), Cl^- (aq); V-Hg^{2+} (aq), $HgCl^+$ (aq), $HgCl_2$ (aq), $HgCl_3^-$ (aq), $HgCl_4^{2-}$ (aq), Cl_2 (aq); VI-Hg^{2+} (aq), $HgCl^+$ (aq), $HgCl_2$ (aq), $HgCl_3^-$ (aq), $HgCl_4^{2-}$ (aq), ClO_4^- (aq); VII-$Hg(OH)_2$ (aq), ClO_4^- (aq); VIII-$Hg(OH)_3^-$ (aq), ClO_4^- (aq).

to the various mercury (II) and chloride complexes or will be reduced to the liquid metallic mercury. Because the solubility of calomel is low, most probably only the small part of it dissolves and forms the mercuric compounds and the rest of it reduces to the metal. The liquid mercury is however relatively harmless (Saunders, 2008; Schmidt, 2013) because it quickly passes through the intestinal tract toward the rectum due to its high density. In the 18th and 19th centuries, both solid calomel and liquid mercury were extensively used as the purgatives (Geffner and Sandler, 1980; Saunders, 2008). Moreover, calomel was very widely used in medicine since the Dark Ages and till the 20th century (Blair et al., 1720; Clay, 1841; Harrison, 1847; Jones, 1888; Beatty, 1899; Patwardhan et al., 2005; Clarkson and Magos, 2006; Schmid, 2008; Bachour, 2015; Gerke, 2015; Preckel, 2015; Sébastia, 2015; Thomann, 2015; Trambaiolo, 2015; Walker, 2015; Wujastik, 2015a,b), and another mercury compound, cinnabar (HgS), which has a behavior in the intestinal tract very similar to that of calomel (Liu et al., 2008; Lu et al., 2011), is still widely used in traditional Chinese medicine (Wong and Koh, 1986; Chi et al., 1993; Espinoza et al., 1995; Bleasdell et al., 1996; Ernst and Coon, 2001; Wong, 2004; Liu et al., 2008; Lu et al., 2011; Zhang et al., 2012). If it had provided a significant lethal effect, it would have caused mass deaths and thus would have been withdrawn from medical usage very quickly. Indeed, mercury is extremely toxic in large doses (Kang-Yum and Oranski, 1992; Chan and Critchley, 1996; Ernst, 1998, 2002; Langford and Ferner, 1999; Davis, 2000; Broussard et al., 2002; Clarkson and Magos, 2006; Wong, 2008; Byard, 2010; Keil et al., 2011; Wu et al., 2013; Yu et al., 2015), and modern medicine does not use it. However, the accurate and careful ingestion of calomel, as patients did two centuries ago, is not harmful.

An implication of calomel in the Napoleon's death is also questionable. Several studies of the specimens obtained from his hairs (Forshufvud et al., 1964; Keynes, 1994, 2004; Weider and Fournier, 1999, 2000; Corso et al., 2000; Lin and Henkelmann, 2003; Lin et al., 2004; Mari et al., 2004; Kintz et al., 2006) indicate that arsenicals rather than mercurials are most likely responsible for it. Probably, Mousavi (2015) overestimated the decisive effect of ingesting calomel as poison resulting in murder in history.

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