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Mercury vapour (Hg^0): Continuing toxicological uncertainties, and establishing a Canadian reference exposure level

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ABSTRACT

There are four published reference exposure levels (RELs) for Hg^0, ranging from 0.09 μg/m^3 to 1 μg/m^3. All RELs were derived from the same toxicological database, predominantly of male chloralkali workers. Some key factors are apparent which make the use of that database questionable for REL derivation. Occupational studies of chloralkali workers are not an appropriate basis for a REL for Hg^0. Concomitant exposure to chlorine gas (Cl_2) diminishes uptake and effects of Hg^0 exposure. There are gender differences in Hg^0 uptake, distribution and excretion, with females at potentially greater risk from Hg^0 exposure than males. Studies of chloralkali workers focused almost exclusively on adult males. Recent investigations of dental professionals (dentists, technicians, assistants) have failed to define a threshold in the dose–response relationship linking Hg^0 with neurobehavioural outcomes, an observation generally ignored in Hg^0 REL development. Finally, there is a growing database on genetic predisposition to health effects associated with Hg^0 exposure. Based on these considerations, we propose a different key study for REL derivation, one that involved male and female dental professionals without concomitant Cl_2 exposure. Adjusting the LOEAL to continuous exposure and applying appropriate UF values, we propose a Canadian REL for Hg^0 of 0.06 μg/m^3.

1. Introduction

Mercury (Hg^0; quicksilver) is a dense silver-white metal that is liquid at room temperature and is characterized by high vapour pressure which is a key determinant of its environmental behaviour and potential for exposure. Hg^0 is known to be present at a wide variety of sites in Canada (as elsewhere), including navigation lightstations (used as liquid bearing for the lens; Wilson et al., 2003; van Netten and Teschke, 1988), surface water level monitoring sites and stations (use of Hg manometers; OAEI, 2000), along oil and gas pipelines (use of Hg manometers to monitor pipeline pressure; Wren and Farrell, 1995), and at historic gold mining sites (used as an amalgamating agent to sequester gold from crushed ore; Parsons et al., 2004). These situations often give rise to non-occupational exposures to Hg^0, as do situations of home contamination due to in-home spills (Hryhorczuk et al., 2006), redevelopment of contaminated industrial buildings for residential use (Orloff et al., 1997), and off-gassing of Hg-containing consumer products (such as paint; Agocs et al., 1990; Beusterien et al., 1991). Such non-occupational exposures must be assessed and managed employing a non-occupational regulatory exposure level (REL) appropriate to the general public and, in particular, children.

Four reference exposure levels (RELs) have been published for Hg^0: 0.3 μg/m^3 (reference air concentration (RfC); US EPA, 2007); 0.2 μg/m^3 (minimal risk level (MRL); ATSDR, 1999); 0.09 μg/m^3 (REL; CalEPA, 2005) and 1 μg/m^3 (air quality guideline as annual average concentration; WHO, 2000). All of these agencies have defined their REL from the same basic toxicology and key study: a lowest-observed-adverse-effect-level (LOAEL) defined variably as 25 μg/m^3 or 26 μg/m^3, based on Fawer et al. (1983). A variety of other studies (e.g., Piikivi and Tolonen, 1989; Piikivi and Hanninen, 1989; Piikivi, 1989; Ngim et al., 1992 and Liang et al., 1993) are generally interpreted as supporting this LOAEL. The numeric differences in the REL values among these agencies appears primarily to be due to differences in the uncertainty factors (UF) and modifying factors (MF) applied in deriving the RELs; i.e., apparently on policy rather than science.

As a result of these inconsistencies, Health Canada's confidence in the current RELs for Hg^0 was low. This paper critically examines certain pharmacokinetic, toxicologic and related issues not previously considered in establishing RELs for Hg^0. Exposure, toxicity,

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pharmacokinetics, etc. are reviewed in detail elsewhere (ATSDR, 1999; WHO, 2000, 2003; etc.) and are not repeated herein. Instead, we focus on the issues and factors that have not been adequately addressed in previous determinations of RELs.

2. Continuing uncertainties

2.1. Interaction of chlorine gas (Cl_2) and Hg^0

Most of the occupational studies underlying our knowledge of Hg^0 toxicity and, therefore, underlying all current RELs for Hg^0, were conducted on chloralkali workers. Although air–Hg^0 concentrations are generally elevated among such workers, concomitant exposure to chlorine gas (Cl_2) occurs. Data on airborne Cl_2 levels in chloralkali plants were recently summarized by the European Union (EU, 2007). Cl_2 levels in the air of chloralkali plants averages about 1 ppm (0.3 mg/m^3) and ranges between 0 ppm and 6.5 ppm (0–19.5 mg/m^3) depending on the specific work environment where sampling was conducted. Earlier reported data also fall within this range, although average levels appeared to be lower. Patil et al. (1970) reported an overall average airborne chlorine concentration in 25 chloralkali plants of 0.15 ppm (range 0.006–1.42 ppm), and Capodaglio et al. (1969; as cited by ACGIH, 2001) reported an average airborne chlorine concentration of 0.30 ± 0.18 ppm.

The concomitant exposure to Cl_2 and Hg^0 effectively reduces worker exposure by decreasing the amount of airborne Hg^0 available for inhalation and absorption. Hg^0 converts to $Hg^{2+}Cl_2^{-1}$ in the presence of Cl_2 at room temperature (Menke and Wallis, 1980; Viola and Cassano, 1968). Also, the inhalation absorption of $HgCl_2$ is only half or less of that of Hg^0 (ATSDR, 1999; Viola and Cassano, 1968). Hg deposition to the brain is also altered. Hg^{2+} (associated with $HgCl_2$) does not effectively cross the blood–brain barrier as does Hg^0 (Lorscheider et al., 1995; Viola and Cassano, 1968). Following Hg^0 exposure, the red blood cell (RBC) to plasma Hg concentration ratio typically ranges between 1:1 and 2:1 (WHO, 1991). However, much less Hg is associated with RBCs in the blood of chloralkali workers (with Cl_2 present). Suzuki et al. (1976), investigating Hg^0-exposed chloralkali workers versus workers from two other industrial sectors (who were all exposed to Hg^0 at similar airborne concentrations (0.01–0.03 mg/m^3)), observed that the RBC to plasma Hg concentration ratio in the chloralkali workers was only 0.02:1 whereas workers of the two other industries (with no concomitant exposure to Cl_2), had RBC to plasma Hg concentration ratios between 1.5:1 and 2:1. A study by Viola and Cassano (1968) of rodents (rats, mice) exposed to Hg^0 alone or in the presence of Cl_2, demonstrated reduced Hg absorption in the presence of Cl_2 and the deposition of Hg to the brain of rodents exposed concomitantly to Hg^0 and Cl_2 was only 1/5th of that when exposure was to Hg^0 alone.

There is other evidence of the interaction of Cl_2 with Hg^0. Cl_2 injection is employed as a direct Hg emissions control technology to reduce Hg^0 levels in industrial stack emissions (Pavlish et al., 2003). Increasing chlorine quantity/concentration in the process improves the efficiency of Hg emission control (Richards, 2005). In the presence of chlorine, Hg^0 is converted to Hg^{2+}, which precipitates with stack particulate matter that is subsequently removed ('scrubbed') from stack emissions.

It is evident that all studies of uptake and toxicity of Hg^0 exposure in chloralkali workers will be potentially confounded by concomitant Cl_2 exposure and, as a result, studies of chloralkali workers should not form the primary basis for a REL for Hg^0; the application and extrapolation of those results to other occupational groups and the general public, whose Hg^0 exposure occurs in the absence of Cl_2, is questionable.

2.2. Gender differences in pharmacokinetics

Most key and supporting studies used to define RELs for Hg^0 relate predominantly or exclusively to adult males. However, there is evidence that males and females respond differently to Hg exposure, in terms of uptake, distribution and excretion. Studies examining both genders have generally exhibited differing accumulation patterns in males and females, with a greater proportion of dose going to the CNS in females. Also, faster elimination rates are observed in males. These differences may result in variable, gender-related toxic response to Hg exposure which must be adequately addressed in the establishment of a REL.

Studies demonstrating gender differences are discussed below. Studies relating to Hg^0 and $HgCl_2$ are discussed owing to similarities in target organ (CNS) and/or excretion.

(1) Hongo et al. (1994) examined urinary Hg excretion by university staff and students who were occasionally exposed to Hg^0 over a period of six years. Gender (along with age and the presence of amalgam fillings) was reported to be an important factor for predicting Hg excretion. They did not, however, specifically or separately quantify the gender-related differences.

(2) Jokstad (1990), in a study of 849 members of the Norwegian Dental Association, observed a slightly but statistically significant lower mean urinary Hg (UHg) level in women compared to men (40 nmol/L versus 44 nmol/L). Confounding factors such as the length of work experience and years in the current office facility did not explain the observed gender difference.

(3) Pamphlett et al. (1997) compared the uptake of inorganic Hg by motor neurons in male and female mice and measured Hg concentrations in their kidneys. Significantly more neurons contained Hg granules in females than in males, and kidneys of males had significantly higher amounts of Hg than those of females. They concluded that the decreased deposition of Hg in the kidneys of the female mice resulted in an increase in circulating Hg, which was available for neuronal uptake.

(4) Pamphlett and Coote (1998) observed Hg in the spinal motor neurons of female mice at half the exposure time (6 h) necessary for it to be observed in the spinal motor neurons of male mice (12 h), following a 50 μg/m^3 exposure.

(5) Nielsen and Anderson (1989, 1990), investigating whole body retention and relative organ distribution of Hg chloride in mice, reported a significantly larger fraction of Hg body burden deposited in the kidneys of males, indicating more rapid renal elimination in males than in females.

(6) Thomas et al. (1986), examining exposures of female and male rats to inorganic Hg, reported the integrated exposure of the brain of female rats to inorganic Hg was 2.19 times greater than that of the males.

(7) Miettnen (1973 as cited in Thomas et al., 1986) reported that the whole body half-time for Hg elimination following ingestion of protein-bound $HgCl_2$ was faster in women than in men.

3. Revisiting the toxicology of Hg^0

3.1. Central nervous system (CNS) toxicity

The US Environmental Protection Agency (US EPA, 2007) based its Hg^0 RfC on Fawer et al. (1983), with supporting evidence being provided by Piikivi and Tolonen (1989), Piikivi and Hanninen (1989), Piikivi (1989), Ngim et al. (1992) and Liang et al. (1993), concerning the CNS effects of Hg^0 exposure. The approach of other agencies with RELs for Hg^0 were similar. However, of these studies, only those of Ngim et al. (1992) and Liang et al. (1993) did not involve chloralkali workers, for whom Hg^0 exposure and uptake would have been potentially confounded by concomitant Cl_2