Disclaimer: This report was the basis for the article appearing in the journal Regulatory Toxicology and Pharmacology (Richardson et al. 2009, Reg Toxicol Pharmacol., 53: 32-38). Please note that the attached report has not been prepared in both of Canada's official languages (french and English); it is available only in English

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# SCIENTIFIC CRITERIA DOCUMENT FOR MERCURY VAPOUR ($Hg^0$): ESTABLISHING A REFERENCE EXPOSURE LEVEL (REL) FOR RISK ASSESSMENT OF $Hg^0$ EXPOSURES IN CANADA

**by**

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***Executive Summary***

The Contaminated Sites Division of Health Canada proposes a ***provisional*** chronic reference exposure level (REL), in the form of a tolerable air-borne concentration, for mercury vapour ($Hg^0$) of 0.06 μg $Hg^0/m^3$ of air. This REL is based on a study conducted by Ngim et al. (1992) in which performance deficits in neuro-behavioural tests were observed in $Hg^0$-exposed 98 Singapore dentists (60 males, 38 females) compared to 54 controls. The geometric mean air-borne Hg concentration in the dental offices at the time of the study (14 $\mu g/m^3$) was interpreted as a lowest-observed-adverse-effect-level (LAOEL). This occupational exposure was adjusted to a time weighted average continuous air concentration of 6 $\mu g/m^3$. Uncertainty factors totally 100 (10 for inter-individual variability; 10 for extrapolation from LOAEL to NOAEL) were applied to the LOAEL to derive the REL.

The REL is designated as provisional owing to significant deficiencies in the toxicological database. In particular, the REL should be re-evaluated once the dose-response relationship with respect to $Hg^0$ and sub-clinical neuro-behavioural effects (following the work of Echeveria and colleagues) can be more precisely quantified.

The reliance of other regulatory agencies on studies by Fawer et al. (1983) and others of workers at chloralkali plants were determined to be unsuitable as the basis for derivation of the REL. In particular, pharmacokinetic and toxicological confounding due to concomitant exposure to chlorine gas within chloralkali plants has not been addressed or considered in previous efforts to establish a REL for $Hg^0$ exposure. Concomitant exposure to chlorine gas and $Hg^0$ reduces the respiratory absorption of Hg and impedes its translocation to the brain where effects occur. The toxicological database was also deemed deficient for studies of gender differences in the pharmocokinetics and toxicological response to $Hg^0$, and fetal exposure and effects following material inhalation exposure to $Hg^0$.

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# 1 INTRODUCTION

## 1.1 Why is a REL for $Hg^0$ Needed?

Mercury vapour ($Hg^0$) is a neurotoxic, renotoxic, immunotoxic substance known to contaminate a wide variety of contaminated sites in Canada, many under the jurisdiction or custodial care of Canadian federal agencies. These sites include:

- navigation light stations where Hg was used as a liquid bearing for the light station lens (Wilson et al., 2003; van Netten and Teschke, 1988);
- hydrometric (water level monitoring) sites and stations where Hg manometers were used in an automated data collection train to monitor surface water levels (OAEI, 2000a);
- various locations along oil and gas pipelines where Hg manometers were used to monitor pipeline pressure levels (Wren and Farrell, 1995);
- historic gold mining sites where $Hg^0$ was employed as an amalgamating agent to sequester gold from crushed ore (Parsons et al., 2004).

For a potential health risk to exist, it is necessary that the Hg exposure from the site exceed the reference exposure level (REL) or toxicological reference value (TRV) that has been deemed, based on current scientific evidence, to be free of possible health effects. Such comparisons are the hallmark of risk assessment (see HC, 2004; US EPA 1989, for examples).

## 1.2 Existing RELs for $Hg^0$

At present, four agencies have established a REL for $Hg^0$, for risk assessment purposes:

- the US EPA (IRIS Database, accessed August 21, 2006), prescribes a tolerable air concentration of 0.3 $\mu g/m^3$;
- the US Agency for Toxic Substances and Disease Registry (ATSDR, 1999) prescribes a minimal risk level (MRL) for chronic inhalation exposure of 0.2 $\mu g/m^3$;
- the California Environmental Protection Agency (CalEPA, 2005) prescribes an inhalation reference exposure level of 0.09 $\mu g/m^3$; and
- the European office of the World Health Organization (WHO, 2000) prescribes a reference exposure level for $Hg^0$, in the form of an air quality guideline, of 1$\mu g$ $Hg^0/m^3$ of air (annual average concentration).

Despite their numeric differences, the RELs of all these agencies are based on the same science; a lowest-observed-adverse-effect-level (LOAEL) defined variably as 25 or 26 $\mu g/m^3$, based on the study of Fawer et al. (1983). A variety of other studies (such as Piikivi and Tolonen, 1989; Piikivi and Hanninen, 1989; Piikivi, 1989; Ngim et al., 1992; and Liang et al., 1993) are interpreted as collaborative evidence supporting this LOAEL. However, the science upon which all these agencies have based their REL values appears dated, despite the apparent recent publication of these agency documents. The key and supporting studies from which the RELs are derived date from the 1980s and early 1990s. The main factor causing numeric differences in the REL values among these

agencies was the application of differing uncertainty factors (UF) and modifying factors (MF) in the final derivation of the REL values.

### 1.3 Evidence for a Need to Revise the Basis of the REL for $Hg^0$

In a review by Ratcliffe *et al.* (1996), a series of criteria were developed to critically evaluate available epidemiological, occupational and toxicological studies of $Hg^0$, towards determining if post-1980s studies provided evidence to warrant revision of the REL for $Hg^0$. That review found several studies that were positive or suggestive of sub-clinical impairment of the CNS. The study of Fawer et al. (1983), the primary basis of all existing REL values, did not meet the criteria on study quality established by Ratcliffe et al. (1996).

Ratcliffe et al. (1996) did not restrict their evaluation to studies of neurotoxicity. They also identified a variety of studies that were positive or suggestive of sub-clinical nephrotoxic effects, occurring in the same general dose range associated with sub-clinical CNS effects.

Additional recent studies have also identified nephrotoxic, neurotoxic and immunotoxic effects associated with $Hg^0$ exposure, reported at dose or exposure levels at or lower than the exposure levels associated with the study of Fawer et al. (1983).

As a result of these factors, confidence in the current reference exposure levels for $Hg^0$ was low, and an evaluation of recent toxicological, epidemiological and occupational studies investigating neurologic, nephrologic and immunologic effects, conducted since 1993, was deemed necessary.

### 1.4 Objectives of This Document

This criteria document considers elemental Hg ($Hg^0$; also known as metallic mercury) only, except where it pertains to levels in bodily fluids and tissues associated with exposure to $Hg^0$.

The objectives of this criteria document were to:

- review sources of $Hg^0$ to, and levels of $Hg^0$ in, the Canadian environment;
- quantify daily exposure to $Hg^0$ by various sectors of the Canadian population;
- critically review and evaluate relevant epidemiological and toxicological studies pertaining to the potential health effects of $Hg^0$; and
- derive a reference exposure level for $Hg^0$ for use in risk assessments of sites contaminated with $Hg^0$ in Canada.

This document does not revisit, repeat or re-evaluate every aspect of Hg exposure, toxicity, pharmacokinetics, etc. These topics are addressed in detail elsewhere (ATSDR, 1999; WHO, 2000, 2003; etc.) and need not be reproduced herein. Instead, this document focuses on:

- new information, published more recently than the science reviewed by other sources and agencies;

- new perspectives or issues deemed inadequately addressed elsewhere, but considered relevant to consider in the establishment of a REL.

# 2 BACKGROUND INFORMATION

## 2.1 What is Mercury?

Mercury (or quicksilver) is a dense silver-white metal which is liquid at room temperature and is characterized by low electrical resistivity, high surface tension, and high thermal conductivity (Andren and Nriagu 1979; CCME, 1999). The physical-chemical properties of $Hg^0$ are presented in Table 1.

Hg is found in the environment, not as the liquid metal, but mainly in the form of amalgams and inorganic salts which have lower vapour pressures than elemental Hg (Andren and Nriagu 1979). The two properties which largely determine the environmental behaviour of Hg are the high vapour pressure of metallic Hg, and the relative insolubility of ionic and organic forms. The vapour pressure of Hg is highly dependent on temperature, and the tendency of liquid Hg to form small droplets increases its rate of evaporation. Hg can exist in three stable oxidation states: elemental Hg ($Hg^0$/Hg(0)), mercurous ion ($Hg_2^{2+}$/Hg(I)), and mercuric ion ($Hg^{2+}$/Hg(II)). Hg (II) forms both inorganic and organic salts, such as chlorides and sulphates, and organo-Hg compounds. Organo-Hg compounds are characterized by covalent bonding of Hg to one or two carbon atoms to form compounds of the type R-Hg-X and R-Hg-R', where R and R' represent the organic moiety, and X represents a halogen. The organic moiety may take the form of alkyl, phenyl and methoxyethyl radicals (WHO 1976). A subclass of short-chained alkylmercurials, which include monomethyl ($CH_3Hg^+$) and dimethyl Hg ($(CH_3)_2Hg$), are the predominant organic Hg compounds found in nature. DimethylHg is less stable and more volatile than monomethyl compounds (CCME, 1999).

## 2.2 Sources to the Canadian Environment

### *2.2.1 Natural source emissions*

$Hg^0$ is released to the Canadian environment from both natural and anthropogenic sources. The release of $Hg^0$ from natural sources to the Canadian atmosphere was recently reviewed and quantified by Richardson et al. (2003). Metals are released into the environment from natural sources through a variety of processes including volcanic eruption, forest and brush fires, evasion from soil, and wind-blown suspension of dust and sea salt spray (Richardson et al., 2003; Lin and Pehkonen, 1998; Nriagu, 1989; among others). Metals generally exist within the atmosphere as a component of particulate matter (de Mora et al., 1993). In the case of Hg, however, the greatest proportion is in the vapour phase, due to its volatility at typical ambient temperatures (de Mora et al., 1993; Schroeder et al., 1995; among others). Nine natural sources of Hg emission to the Canadian atmosphere were quantified by Richardson et al. (2003):

1 $Hg^0$ flux from soils and bedrock;
2 $Hg^0$ flux from surface marine waters;
3 $Hg^0$ flux from surface fresh waters;
4 volcanic emissions (both gaseous and particulate Hg);
5 wind-induced entrainment of surficial soil and dust particles (particulate Hg);
6 wind-induced entrainment of sea salt spray (particulate Hg);
7 forest and brush fires (both gaseous and particulate Hg);
8 meteoritic (extra-terrestrial) dust (particulate Hg);
9 $Hg^0$ flux directly from vegetation (biogenic emissions ).

Total annual natural $Hg^0$ emissions to the Canadian atmosphere are summarized from Richardson et al. (2003) in Table 2; emissions of particulate Hg ($Hg^{2+}$) have been omitted.

### *2.2.2 Anthropogenic emissions*

In Canada, anthropogenic Hg releases can be attributed to mining and smelting operations, waste incineration, coal combustion, the chloralkali industry, amongst other sources. A total of about 8 tonnes of Hg was released in the Canadian atmosphere in the year 2000 (EC, 2002a), the last year for which data were available. Total annual anthropogenic Hg emissions to the Canadian atmosphere for the year 2000 are summarized in Table 3. Annual trends since 1990 of Canadian anthropogenic atmospheric releases of Hg (from EC, 2002b) are presented in Table 4.

Anthropogenic release of $Hg^0$ also results from the use of dental amalgam in Canadian dentistry (Van Boom et al., 2003; Trip, 2001; OAEI, 2000b). Dental amalgam, a primary dental restorative material, is a mixture of metals consisting of approximately 50% metallic Hg, by weight, mixed with an alloy containing varying amounts of silver (up to 70%), copper (up to 30%) and tin (up to 30%), among other potential components (Berry et al. 1994). In 1999, 1642 kg of Hg were imported into Canada as a component in amalgam dental materials (Van Boom et al., 2003), down from 2129.5 kg in 1994 (Richardson and Allan, 1996).

In the dental office, the grinding, drilling and polishing of amalgam results in the production of fine particulate matter, which is collected by chair-side oral evacuation systems and discharged to dental clinic wastewater streams. Excess amalgam remaining after placement of a new filling may simply be discarded in clinic trash. As a result of these and other waste management practices (reviewed by OAEI, 2000b), amalgam-related Hg is discharged to the environment by dental clinics, a portion of which enters the atmosphere.

The presence of amalgam fillings in members of the Canadian population also increases the levels of Hg in their urine, with urinary Hg (UHg) concentrations and output increasing with increasing numbers of amalgam fillings (reviewed by Richardson and Allan, 1996). Likewise, Hg levels in faeces are elevated in persons with amalgam fillings, and faecal Hg output increases with increasing numbers of amalgam fillings (Skare and Engqvist, 1994; Skare, 1995). As a result of elevated Hg levels in urine and faeces in relation to amalgam fillings, amalgam-related Hg is contributed to

residential wastewater through human excrement (OAEI, 2000b), a portion of which enters the atmosphere.

It was estimated that, in 1999, some 1879 kg of Hg , incorporated in scrap and particulate amalgam, was discharged by Canadian dental clinics, 530 kg of which was $Hg^0$ emitted to the atmosphere due to incinerator emissions and volatilization from sewage sludge applied to farmland (Van Boom et al., 2003; OAEI, 2000b). A further 112 kg of amalgam-related Hg was discharged to residential municipal wastewater systems due to Hg content of urine and faeces of the Canadian population with amalgam fillings, 28 kg of which was ultimately emitted to the atmosphere (OAEI, 2000b). All Canadian dental-related Hg emissions estimated for 1999 are summarized in Table 5. It should be noted that the implementation of the CCME Canada-Wide Standard on Mercury for Dental Amalgam Waste, introduced in 2001 (CCME, 2001), should result in the reduction of environmental releases of Hg from dental clinics.

## 2.3 Levels in the Environment

The only relevant environmental media pertaining to exposure to $Hg^0$ are ambient air and indoor air. The forms of Hg in all other media are dominated by ionic Hg ($Hg^{2+}$) or methyl Hg.

### *2.3.1 Ambient (Outdoor) Air*

#### *Canada*

Data on the concentrations of Hg (as total gaseous mercury; TGM) in Canadian ambient air from non-urbanized areas is offered by the Canadian Atmospheric Mercury Measurement Network (CAMNet). CAMNet has 11 sites located in rural or background locations in British Columbia (Reifel Island), Alberta (Fort Chipewyan, Esther), Saskatchewan (Bratts lake), Ontario (Burnt Island, Egbert, Point Petre), Quebec (St. Anicet), New Brunswick (St. Andrews), Nova Scotia (Kejimkujik National Park) and Nunuvut (Alert). CAMNet data on daily average TGM concentration, spanning its inception in 1995 through December 2005, are summarized by Temme et al. (2006).

CAMNet data are reported for airborne concentrations of total gaseous mercury (TGM), which is predominantly $Hg^0$, but may also include trace amounts of reactive gaseous mercury species (Temme et al., 2006). Overall, the daily average TGM concentration averaged 1.58 $\pm$ 0.17 ng/m$^3$ across all sites and all years (range: 0.21 - 2.75 ng/m$^3$; n = 3959). This was essentially the same as previously reported for the same network. Kellerhals et al. (2003) reported an overall average median atmospheric concentration for $Hg^0$ of 1.60 $\pm$ 0.15 ng/m$^3$ (average of site median values) for ten rural Canadian sites from 1997-1999. Average levels ranged from 1.32 to 1.83 ng/m$^3$ among the sites.

TGM concentration fluctuates seasonally, with slightly higher levels in winter and spring relative to summer and fall (Temme et al., 2006; Kellerhals et al., 2003). TGM concentration also

apparently fluctuates diurnally, at least at some sites, with levels recorded between 16:00 and 24:00 hours being higher than levels recorded between 4:00 and 12:00 hours (Tordon et al., 2005).

Publications concerning TGM data of the CAMNet have been quite consistent over time. The three monitoring sites near the Canadian Great Lakes (Kim et al., 2005) had overall average levels for the years 1997-2000 of 1.93 ± 0.44 ng/m$^3$ (Point Petre, ON), 1.69 ± 0.32 ng/m$^3$ (Egbert, ON) and 1.58 ± 0.23 ng/m$^3$ (Burnt Island, ON). The slight elevation of average TGM concentration in winter and spring relative to summer and fall were also observed but only at two of the three sites reported by Kim et al. (2005).

Beauchamp et al. (1997) reported TGM levels in air for the two sites in Atlantic Canada (Kejimkujik National Park and St. Andrews, New Brunswick) from investigations conducted in 1996. Concentrations of TGM at Kejimkujik National Park ranged from 0.51 to 2.9 ng/m$^3$ with an annual median concentration of 1.52 ng/m$^3$. St. Andrews had a median concentration of 1.5 ng/m$^3$. An examination of TGM data for these two sites from 1996 through 2003 (Tordon et al., 2005) revealed that annual mean TGM levels ranged between 1.30 and 1.64 ng/m$^3$ at Kejimkujik during this time period, and annual mean levels at St. Andrews ranged between 1.2 and 1.56 ng/m$^3$.

Earlier Canadian studies of $Hg^0$ levels in the atmosphere include Schroeder and Jackson (1987) who reported concentrations of several Hg species in the air in and around Toronto, Ontario during the fall of 1981. The limited data (total n=25) indicated a minimum of 3 ng Hg/m$^3$, a maximum of 27 ng Hg/m$^3$ and a mean of 10 ng Hg/m$^3$. Also, OMEE (1994) reported 11 to 18 serial half hour measurements of total Hg in the air of Windsor, Ontario on six consecutive days from July 25 to August 2, 1990. Individual half hour air concentrations ranged from below detection (n=1; detection limit = 10 ng Hg/m$^3$) to 160 ng Hg/m$^3$. Daily arithmetic averages ranged from 19.3 to 45.6 ng Hg/m$^3$, with a grand arithmetic mean of 28.8 ± 19.9 ng Hg/m$^3$.

*United States*

Some data and information for the US are included for comparison to available Canadian data. The values reported by Kim et al. (2005), Kellerhals et al. (2003) and Beauchamp et al. (1997) compare well with the estimated ambient air-borne Hg concentration employed by the US EPA in their Mercury Study Report to Congress (US EPA, 1997a), in which an air concentration of 1.6 ng/m$^3$ was assumed for the assessment of Hg exposure due to ambient air inhalation. However, no specific summary of airborne Hg concentration data was presented in the Mercury Study Report to Congress.

Hopke et al. (2003) reported outdoor air $Hg^0$ concentrations for rural sites in Potsdam and Stockton in New York State, measured during the summers of 2000 and 2001. For 2000, the mean ambient air concentration of $Hg^0$ in Potsdam was 2.4 ± 1.2 ng/m$^3$ (n=93) whereas the average concentration at Stockton was 1.2 ± 1.0 ng/m$^3$ (n=60). In 2001, the mean concentrations were 1.1 ng/m$^3$ and 1.6 ng/m$^3$ at Potsdam and Stockton, respectively.

In north central Wisconsin, at the Crab Lake Atmospheric Mercury Station, $Hg^0$ concentrations ranged between 1.21 ± 0.49 ng/m$^3$ and 1.8 ± 0.4 ng/m$^3$ between August 1992 and May 1994

(Lamborg et al., 1995). At Underhill Center, VT in 1993, the average $Hg^0$ concentration in ambient air was 2.0 (range: 1.2 - 4.2; n=91) ng/m$^3$ (Burke et al., 1995). A site in Acadia National Park, Maine, used by Beauchamp et al. (1997) for comparison to two Atlantic Canada sites (Kejimkujik National Park and St. Andrews, NB) had a median annual air concentration of 1.73 ng/m$^3$ in 1996.

Generally elevated $Hg^0$ levels are routinely reported in urban areas relative to rural and remote locations. Outdoor Hg levels were recorded in 37 generally unspecified urban locations (other than "in proximity to the buildings evaluated") during an investigation of buildings in New Jersey contaminated with Hg metal due to cultural Hg use (Garentano et al., 2006). The reported average outdoor concentration was 5 ± 5 ng/m$^3$. Pirron et al. (1995) reported 1992 airborne levels of $Hg^0$ of 48.8 ng/m$^3$ in Detroit, MI northwest of the Detroit municipal waste incinerator, and 3.4 ng/m$^3$ at Zug Island in Detroit, an area not impacted by the incinerator but affected by local urbanization.

### *2.3.2 Indoor Air*

No published or unpublished data were located on Hg levels in indoor air of Canadian homes.

Carpi and Chen (2001) reported indoor air Hg concentrations from 12 indoor sites in and around metropolitan New York, that were not specifically known to be contaminated with Hg. Individual measurements ranged between 6.5 and 532 ng/m$^3$, with site-specific average indoor air concentrations ranging from 4.25 ± 1.0 (± 95% CI; not standard deviation) to 522.78 ± 6.1 ng/m$^3$. The overall mean indoor air Hg concentration was 69 ng/m$^3$. Eleven of the 12 sites sampled in this study showed levels of airborne Hg that were significantly elevated over outdoor concentrations.

The average level reported by Carpi and Chen (2001) compares well with the median indoor air $Hg^0$ concentration of 50 ng/m$^3$ reported by Hudson et al. (1987) for 39 non-contaminated homes selected for comparison of indoor air $Hg^0$ concentrations with 38 homes of persons working with Hg occupationally.

Hudson et al. (1987) found a median $Hg^0$ indoor air concentration of 240 ng/m$^3$ in the homes of persons working with Hg metal, and who apparently inadvertently transport Hg contamination home on clothing, etc. Levels in other buildings where Hg metal may be used and spilled are similarly high. Individual indoor levels reported from a total of 67 buildings (some multifamily residential buildings), subject to contamination through the cultural use of Hg metal, ranged up to 2,022 ng/m$^3$ (Garentano et al., 2006), with the highest indoor average concentration being 299 ng/m$^3$.

Hryhorczuk et al. (2006) reported on $Hg^0$ concentrations in indoor air of 171 Illinois homes where Hg had been spilled during the removal of older gas regulators. Indoor levels averaged approximately 10 µg/m$^3$ in 165 of the homes where residents' urinary Hg (UHg) levels were < 10 µg/L (interpreted by the authors as no apparent Hg exposure, although it is still assumed that a Hg spill had occurred), whereas indoor air levels averaged > 25 µg/m$^3$ in 6 homes where residents' UHg levels were ≥10 µg/L. Note that average airborne $Hg^0$ concentrations were not reported by Hryhorczuk et al. (2006) but were deduced from a frequency histogram depicting numbers of residences per specified $Hg^0$ concentration intervals.

Orloff et al. (1997) investigated Hg contamination of a residential condominium complex previously used for industrial purposes where Hg was employed. On various dates in 1995, from various residential units, $Hg^0$ levels in breathing zone air ranged from 4 to 45 $\mu g/m^3$. Levels in stairways on one date ranged from 12 to 18 $\mu g/m^3$. $Hg^0$ concentrations measured at floor level, or at junctions of walls and floors (likely areas of hidden elemental Hg) were higher; the highest concentration of 888 $\mu g/m^3$ was associated with the subflooring of the $5^{th}$ floor.

Previous studies have reported indoor air contamination with $Hg^0$ as the result of the use of Hg compounds as preservatives for indoor latex paint. Agocs et al. (1990) and Beusterien et al. (1991) reported indoor air Hg data for 10 homes in Michigan (1989) and 16 homes in Ohio (1990), respectively, where no Hg-containing paint had been applied within the preceding 18 months. In both studies, the median Hg levels were non-detected when measured by atomic absorption spectrophotometry (reported detection limit (DL)=0.5 $nmol/m^3$). Analysis of 4 homes by cryogenic gas chromatography with atomic fluorescence detection (reported DL = 3 $ng/m^3$) measured Hg at a median level of 52 ng $Hg/m^3$ (range: 36-107 ng $Hg/m^3$) (Beusterien et al., 1991). It should be noted that the use of Hg as a preservative in interior paint was voluntarily discontinued in Canada in January 1991 (Richardson and Allan, 1996).

*Summary: Indoor air levels of $Hg^0$*

Although no Canadian data exist on concentrations of $Hg^0$ in indoor air, data from the United States suggest that indoor levels will generally range between 10 to 25 $\mu g/m^3$ (and possibly higher) in homes with some inadvertent source of $Hg^0$ contamination, with levels dependent on source strength and proximity to breathing zone air. For uncontaminated homes, however, indoor airborne levels of $Hg^0$ appear to average about 50 $ng/m^3$ (0.05 $\mu g/m^3$).

## 3 HUMAN EXPOSURE ESTIMATES

Exposure to $Hg^0$ arises from 3 primary sources (WHO, 2000):

- ambient (outdoor) air;
- indoor air;
- dental amalgam.

Exposure to Hg by the Canadian population has been variously quantified by Richardson et al. (1995), Richardson and Allan (1996) and Health Canada (1998). Estimated daily intakes of $Hg^0$ by 5 age groups of the Canadian population, based on the most recently available data and information, are presented in Table 6. Dental amalgam is a significant source of $Hg^0$ exposure (see Table 6; WHO, 2000), although this source is only directly relevant to those persons possessing such fillings.

### 3.1 $Hg^0$ Exposure from Dental Amalgam

The overall rate in Canada of amalgam use as a dental filling material in 1996 was about 40% of fillings placed, but ranged from 38% to 62%, depending on the province or territory or residence (P. Neufeld, Health Canada, pers. com. cited by OAEI, 2000b). This rate of use was significantly reduced relative to the 1980's when dental amalgam comprised between 75% and 80% of all fillings in the North American population (Jones, 1993). More recent data on dental amalgam use in Canada were not available, but it is anticipated that amalgam use continues to decline with the increasing popularity of 'aesthetic' (white) dental filling materials (Adegbembo and Watson, 2005).

$Hg^0$ is released from amalgam fillings and is routinely detected in exhaled or intra-oral air (Gay et al. 1979; Svare et al., 1981; Patterson et al. 1985; Vimy and Lorscheider, 1985; Berglund et al. 1988; Jokstad et al. 1992), at concentrations which increase with the number of filled teeth (Svare et al. 1981; Vimy and Lorscheider 1985; Patterson et al. 1985; Jokstad et al. 1992).

$Hg^0$ released from amalgam fillings is absorbed with air inhaled through the mouth (Richardson and Allan, 1996), with $Hg^0$ exposure increasing in relation to the number of amalgam fillings. $Hg^0$ exposure from amalgam has been reviewed in detail and quantified for Canada by Richardson (1995; see also Richardson and Allan, 1996). No less than 13 analyses have been conducted and published on amalgam-derived $Hg^0$ exposure in persons with amalgam fillings (see Richardson, 2003), with more recent estimates generally agreeing that exposure ranges between 3 and 10 μg/day on average, with overall exposure ranging up to perhaps 12 to 15 μg/day for persons with up to 25 amalgam-filled teeth (see Richardson, 2003).

Concentrations of Hg in urine, a biomarker of inhalation exposure (Tsuji et al., 2003; WHO, 1991), are higher in individuals with amalgam fillings than in those without, and correlate positively with number of filled teeth, number of filled tooth surfaces, number of filled occlusal surfaces, total amalgam surface area, or other indices of amalgam load (Aronsson et al. 1989; Akesson et al. 1991; Skerfving 1991; Langworth et al. 1991; Jokstad et al. 1992; Svensson et al. 1992; Suzuki et al. 1993; Herrmann and Schweinsberg 1993; Schweinsberg 1994; Skare and Engqvist 1994; Kingman et al., 1998). Hg levels in other tissues also increase with increasing amalgam load, including blood (particularly blood plasma) (Abraham et al. 1984; Snapp et al. 1989; Molin et al. 1990; Akesson et al. 1991; Jokstad et al. 1992; Svensson et al. 1992; Herrstrom et al. 1994), kidney (Nylander et al. 1987), brain (Friberg et al. 1986; Nylander et al. 1987; Eggleston and Nylander 1987; Weiner and Nylander 1993), pituitary gland (Nylander et al. 1989; Weiner and Nylander 1993), abdominal muscle (Weiner and Nylander 1993) and oral mucosa (Willershausen-Zonnchen et al. 1992). Urine and blood Hg levels decline after amalgam removal (Snapp et al. 1989; Molin et al. 1990; Skerfving, 1991). The amount of Hg excreted as a result of chelation therapy increased as the number of amalgam fillings increased (Aposhian et al. 1992; Herrmann and Schweinsberg 1993), with about two thirds of the body burden of excretable Hg associated with exposure arising from amalgam fillings (Aposhian et al. 1992).

The human fetus is exposed to $Hg^0$ originating from maternal amalgam fillings. Levels of Hg in amniotic fluid have been shown to be positively associated with maternal amalgam fillings, increasing as the maternal load of amalgam fillings increases (Luglie et al., 2005). Drasch et al. (1994) found statistically significant positive associations between the number of maternal amalgam

fillings and the levels of Hg in: a) fetal liver; b) fetal renal cortex; c) the renal cortex of older infants (11-50 weeks old); d) the cerebral cortex of older infants. Levels of Hg specifically in fetal brain tissue were not reported.

Transfer of Hg from maternal amalgam to the fetus has also been observed in sheep (Vimy et al. 1990) implanted with amalgam fillings. Likewise, transfer of Hg to the fetuses of guinea pigs (Yoshida et al. 1986, 1990), rats (Clarkson et al. 1972) and mice (Khayat and Dencker 1982) results from exposure of pregnant female animals to Hg vapour.

$Hg^0$ originating from amalgam fillings is passed to infants via breast feeding. Drasch et al. (1998) found that the Hg concentration in 70 breast milk samples from 46 mothers correlated positively with the number of maternal amalgam-filled teeth. An earlier study by Klemann et al. (1990) found no correlation between maternal dental amalgam status and Hg levels in breast milk. However, that earlier study failed to control for fish consumption or other factors that would confound the association between breast milk Hg levels and amalgam status.

Animal models have also demonstrated the transfer of Hg to breast milk following exposure of guinea pigs to Hg vapour (Yoshida et al. 1992). Hg arising specifically from dental amalgam was detected in the milk of sheep (Vimy et al. 1990).

## 4 PHARMACOKINETICS (UPTAKE, RETENTION, TISSUE DISTRIBUTION, EXCRETION)

A review of Hg vapour metabolism is provided by Lorscheider *et al.* (1995), while the pharmacokinetics of Hg have been reviewed in detail by ATSDR (1999) and WHO (2000, 2003). Exposure to $Hg^0$ is via the lung, with reported absorption ranging from 61 to 86% of the vapour inhaled (Neilsen-Kudsk 1965; Teisinger and Fiserova-Bergerova 1965; Hursh et al. 1976; Oikawa et al. 1982).

The primary organ of deposition is the kidney, with lesser amounts in the liver, CNS and other tissues (WHO 1991). The ratio of plasma:erythrocyte Hg concentrations is approximately 1 or 2 for $Hg^0$ (WHO 1991), compared to 0.05 for methylHg (WHO 1990). WHO (1991) concluded from *in vitro* studies of Hg oxidation in blood (Hursh et al. 1988) that transport from the lung to the blood-brain barrier is direct and rapid with little oxidation (<10%) of $Hg^0$ to $Hg^{2+}$ before reaching the blood-brain barrier. $Hg^0$ crosses the blood-brain barrier (WHO, 2003) where it is subsequently oxidized to $Hg^{2+}$ (Lorscheider et al., 1995). $Hg^{2+}$ can not readily cross the blood-brain barrier (WHO, 2003) and is thereby 'trapped' in the brain or CNS (Lorscheider et al. 1995). A greater proportion of $Hg^0$ absorbed via the lung is deposited in the brain than for any other route of exposure or form of Hg (WHO 1991). The concentration of Hg in brain tissue has been found to correlate with the number of amalgam fillings (primary source of $Hg^0$ exposure) in the person's teeth (Friberg et al. 1986; Nylander et al. 1987; Eggleston and Nylander 1987; Weiner and Nylander 1993), but fetal brain tissue generally contains lesser Hg than the mother following maternal inhalation exposure to $Hg^0$ (Warfinge, 2000).

Excretion of Hg following exposure to Hg vapour is predominantly via urine and faeces, although a small proportion of excretion may also occur via expired air, saliva, sweat and breast milk (WHO 2003). Urinary excretion appears to predominate for high (occupational) exposure (WHO 1991). Although Skare and Engqvist (1994) reported up to 10 fold greater excretion of Hg via faeces than via urine over a 24 hour period for a group of subjects with amalgam fillings, it is unclear what proportion of this Hg in the faeces represented systemically-absorbed and excreted Hg versus particulate and inorganic Hg passing through the gastrointestinal tract.

Hg vapour is ultimately converted to $Hg^{2+}$ in the body (Lorscheider *et al.* 1995) and its whole body elimination is, therefore, the same as that for $Hg^{2+}$. Using whole body measurements, Skerfving and Vostal (1972) found that the elimination of mercuric salts in human subjects had a biological half-life of 30 to 60 days. No sex difference in body burden was noted. The half lives of other forms of Hg in humans are similar (WHO 1991). However, there is some evidence that the half-life in the brain may be longer than that in the rest of the body (US EPA 1985; Piotrowski and Inskip 1981). Modelling of Hg accumulation and elimination in the brain suggests that a small elimination phase may exist, having a half life approaching 30 years (Bernard and Purdue, 1984).

Urinary excretion is a significant route of Hg excretion, considered the primary route (58%) following long term inhalation exposure (WHO, 2003). However, the proportion of Hg excreted by the urinary route is dose dependent at lower exposure levels (Rothstein and Hayes, 1960, 1964; Cember, 1962; Morcillo and Santamaria, 1995). This phenomenon is most readily apparent in the curvilinear relationship between number of amalgam fillings (primary non-occupational source of exposure to $Hg^0$) and Hg concentration in urine (see data reported by Skerfving (1991), Herrmann and Schweinsberg (1993), Langworth *et al.* (1988, 1991), and Akesson *et al.* (1991)). As exposure level (number of amalgam fillings) increases, the proportion of Hg excreted in urine also increases, producing the observed curve. Based on published evidence, Richardson (1998) determined that the proportion of daily Hg excretion by the urinary route increases progressively from about 10% for a dose of 0.2-0.45 μg/day, to 40% for persons receiving a daily dose of 9-12 μg/day.

### 4.1 Gender Differences in Hg Pharmacokinetics

Several authors have indicated that gender is an important factor in the metabolic and toxicologic response to exposure to chemicals (Calabrese, 1986; Silvaggio and Mattison, 1994; Gochfeld, 1997; Iyaniwura, 2004). There is some evidence that males and females may respond differently to Hg exposure, in terms of uptake, distribution, and toxicity. As discussed below, studies examining both genders have exhibited differing accumulation patterns in males and females, and faster elimination rates in males. These differences may result in variable, gender-related toxic response to Hg exposure. The available data, however, are limited and inadequate to reliably quantify gender-related differences in toxicity.

It should be noted that both organic (methyl Hg) and inorganic forms of Hg were considered in this review of gender-specific response because once across the blood-brain barrier the ultimate biochemical fate of the ionic Hg moiety ($Hg^{2+}$ from organic and inorganic Hg) is identical (Lorscheider et al., 1995).

Hongo et al. (1994) examined urinary Hg excretion by university staff and students who were occasionally exposed to Hg vapour over a period of six years. Regression analysis indicated that the Hg vapour exposure level was the major variable predicting urinary Hg excretion, but gender (along with age and the presence of amalgam fillings) was also reported to be an important factor. They did not, however, specifically quantify the gender-related differences.

Jokstad (1990) surveyed the Norwegian Dental Association to assess the significance of potential sources of Hg exposure. Urinary Hg excretion values were correlated to answers on the survey. In addition to correlations between environment and practice characteristics and Hg excretion values, the data indicated that urinary Hg excretion might be gender-dependent, due to the fact that the mean UHg levels of 849 participants were slightly lower in women compared to men (40 nmol/L versus 44 nmol/L). When a group of female assistants with higher exposures were excluded from the analysis, the average UHg concentration for women dropped to 38 nmol/L. The authors reported, "[n]either the length of work experience, nor the years in the current office facility correlate[d] with the urinary Hg levels." While there was a correlation between UHg concentrations and the number of hours spent per week in the clinic for the entire group and for the male participants, this correlation was not observed when female participants were evaluated alone. The mean Hg concentrations for females remained relatively constant and, for the most part, were lower than those measured in the male participants, especially at the higher exposure levels. The authors did not offer a definitive conclusion as to whether their results support gender-dependency in absorption or excretion.

At an annual American Dental Association (ADA) meeting, Kaste et al. (1992) presented a study of dentists and dental assistants who had been evaluated for Hg exposure. Over 4000 participants (7.6% women) answered questionnaires and provided urine samples. There was a small difference in average UHg concentration (4.9 μg/L in women and 6.3 μg/L in men). This variation might, however, be attributable to the number of years of exposure as Kaste et al. (1992) reported an average of 8.2 years in practice for the female participants and an average of 19.2 years in practice for the males.

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 female mice than in male mice, and kidneys of male mice had significantly higher amounts of Hg when compared to the females. Pamphlett et al. (1997) 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 neuron uptake.

Pamphlett and Coote (1998) were interested in identifying the lowest dose of Hg vapour that resulted in Hg deposition in neurons, and in determining if female neurons were more susceptible to Hg vapour toxicity than male neurons. After a 50 $\mu g/m^3$ dose, Hg was observed in the spinal motor neurons of female mice at half the exposure time (6 hours) necessary for it to be observed in the spinal motor neurons of male mice (12 hours).

Nielsen and Anderson (1990) investigated the effects of different dose levels and routes of administration on whole body retention and relative organ distribution of Hg chloride in two strains of female mice. In addition, the authors investigated gender differences in the distribution of Hg chloride by comparing their results to a previous study with male mice (Nielsen and Andersen, 1989). This comparison showed that similar fractions of Hg body burden were distributed in the liver of males and females, while a significantly larger fraction of Hg body burden was deposited in the kidneys of the male mice than in female mice.

Thomas et al. (1986) examined the integrated exposures of tissues of female and male rats to organic and inorganic Hg. While whole body comparisons indicated that integrated exposures of males and females to inorganic Hg were equal, this study demonstrated that the integrated exposure of the brain of female rats to inorganic Hg was 2.19 times that of the males. This finding suggested that there was a gender-related difference in the accumulation and/or retention of inorganic Hg in the central nervous system.

Miettnen (1973 as cited in Thomas et al., 1986) reported that, in humans, the whole body half time for Hg elimination following ingestion of protein bound Hg chloride was faster in females than in males.

Hirayama and Yasutake (1986) and Yasutake and Hirayama (1988) studied C57BL/6N and BALB/cA mice to evaluate the mechanisms for gender-related differences in the *in vivo* fate of methyl Hg. A single administration of methyl Hg chloride in mature mice resulted in higher levels of Hg in urine of males than of females. Five minutes post exposure, Hg levels in male kidneys were higher than in female kidneys and these higher male concentrations were still in evidence after 24 hours. Lower Hg values were reported in other tissues of males when compared with females. After 24 hours the Hg levels in urine were 6.5 times higher in males than in females. The levels of Hg in kidneys for males were higher than in females whereas the females had higher Hg levels in the brain, liver and plasma. Castrated males had Hg tissue levels similar to females except in the brain and castrated females exhibited decreased urinary excretion of Hg. The authors concluded, "tissue distribution and urinary excretion of the administered methyl Hg seem to be subject to sex hormone control. This study demonstrates that the metabolism and elimination of methyl Hg occur significantly faster in males and that the sequence of events leading to urinary excretion of methyl Hg may proceed under the control of sex hormones."

Magos et al. (1981) compared the sensitivity of female and male rats to methyl Hg. "After identical doses the brains of females always contained more Hg than those of males. Female rats developed more intensive co-ordination disorders and after five doses they had more extensive damage in the granular layer of the cerebellum than males." However, the regional distribution of Hg within the brain was the same in males and females. The elimination rate in male kidneys was found to be significantly faster (16 day half-life) than the elimination rate for female kidneys (37 day half-life).

Nielsen and Andersen (1991) found the route of methyl Hg administration did not affect the whole-body retention of Hg significantly but that female mice retained more Hg than did male mice.

Kidney deposition in males was twice that in females, and the male mice excreted Hg significantly faster than did the females.

Although most studies indicate faster clearance in males than in females, Thomas et al. (1986) found a higher average concentration of organic Hg in the kidneys of the females, and adult females treated with methyl Hg displayed a faster rate of whole body clearance than did males.

### *4.1.1 Summary and conclusions: gender differences*

Based on the foregoing, the evidence indicates clear gender differences in uptake, distribution, and excretion of $Hg^0$. However, the evidence is too limited for quantitative evaluation. Most of the studies reviewed indicate that males metabolize and eliminate Hg more quickly than do females and that, after exposure, Hg tends to be distributed differently in males and females, with a greater proportion of dose going to the brain and CNS of females. While Hg appears to be distributed more quickly to the kidney and urine in males, it appears to be retained for a longer time in females and thus be potentially more available to illicit toxic response.

## 4.2 Interaction of Chlorine Gas and $Hg^0$

A large proportion of the occupational studies underlying our knowledge of $Hg^0$ toxicity, and subsequently underlying all current RELs for $Hg^0$, were conducted on workers in the chloralkali industry. Although Air-$Hg^0$ concentrations are generally elevated for workers in this industry, it is also true that concomitant exposure to chlorine gas occurs.

Recent data on airborne chlorine levels in the work environment of chloralkali plants could not be found. Patil et al. (1970) reported an overall average airborne chlorine concentration in 25 chloralkali plants of 0.15 ppm (range 0.006 to 1.42 ppm). Capodaglio et al. (1970; as cited by ACGIH, 2001) reported an average airborne chlorine concentration of 0.30 ± 0.18 ppm. It is anticipated that current conditions will be similar, given that the occupational exposure limit (TLV) for chlorine is 0.5 ppm (ACGIH, 2001) and reported average levels were below that limit.

Chlorine gas is known to interfere with the measurement of airborne levels of $Hg^0$ (McCammon and Woodfin, 1977), and $Hg^0$ is converted to $HgCl_2$ in air in the presence of chlorine gas (Menke and Wallis, 1980; Viola and Cassano, 1968). The inhalation absorption of $HgCl_2$ is perhaps only half or less of that of $Hg^0$ (ATSDR, 1999; Viola and Cassano, 1968). $Hg^{2+}$ (associated with $HgCl_2$) does not effectively cross the blood-brain barrier as does $Hg^0$ (Lorscheider et al., 1995; Viola and Cassano, 1968). As a result, an absorbed dose of inhaled $HgCl_2$ will not enter the CNS in significant proportion relative to the total inhaled dose, and subsequently will not illicit the same magnitude of CNS effects relative to the same dose of inhaled $Hg^0$.

There is other evidence of the interaction of chlorine gas with $Hg^0$. The effectiveness of chlorine gas to react with $Hg^0$ is a key component of $Hg^0$ stack emission control technologies. Chlorine gas 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.

The interference of concomitant $Hg^0$ and chlorine gas exposure has not been investigated in the literature with respect to the potential impact on toxicological outcomes of Hg exposure. However, there is some indirect evidence of this potential interference. Suzuki et al. (1976) investigated $Hg^0$-

exposed workers from 3 industrial sectors who were all exposed to $Hg^0$ at similar airborne concentrations (0.01 to 0.03 mg/m3). The authors noted that Hg in the blood of those workers of the chloralkali sector was predominantly associated with the red blood cells, and observed a red cell to plasma ratio of 0.02 in chloralkali workers. For workers of two other industries, the proportion of Hg associated with red blood cells was 4 to 5 times higher, and the ratio of red cell Hg to plasma Hg was 1.5-2. A study by Viola and Cassano (1968) demonstrated reduced overall Hg absorption, and significant differences in tissue distribution, when rodents (rats, mice) were exposed to $Hg^0$ alone or in the presence of chlorine gas. The deposition of Hg to the brain of rodents exposed concomitantly to $Hg^0$ and chlorine gas was only 1/5th of that when exposure was to $Hg^0$ alone.

Any interference that might result from concomitant exposure to $Hg^0$ and chlorine gas would reduce the total quantity of Hg absorbed, and the quantity of Hg entering the CNS to illicit effects. As a result, CNS impairment reported for chloralkali workers may be diminished relative to other occupational groups that are exposed to similar $Hg^0$ levels but in the absence of chlorine gas. Although this factor cannot be adequately quantified at this time, caution must be exercised in the interpretation of CNS effects and dose-response relationships measured in chloralkali workers. The application and extrapolation of those results to other occupational groups and the general public, such as to establish a REL, is questionable.

It was concluded that the application of occupational health studies of chloralkali workers to establish a REL for $Hg^0$ should be avoided where feasible, until such time as the influence of concomitant chlorine gas exposure on Hg exposure, absorption, and tissue distribution can be investigated and quantified. In particular, quantitative data are required on:

- the concomitant levels of $Hg^0$, $HgCl_2$ and chlorine gas to which chloralkali workers are exposed in workroom air (and/or were exposed in previous occupational health studies);
- the rate and extent of systemic absorption of $Hg^0$ and $HgCl_2$ from occupational environments in these workers; and
- the total proportion of delivered and absorbed Hg dose that is available to cross the blood-brain barrier (to illicit CNS effects).

## 5 TOXICOLOGY

The toxicology of $Hg^0$ has been reviewed in detail elsewhere (ATSDR, 1999; WHO, 2003). The focus of this document is on more recent studies relevant to determining a reference exposure level for $Hg^0$, and on those aspects of $Hg^0$ toxicity that influence the determination of appropriate uncertainty factors (UF) and modifying factors (MF) when deriving the REL.

A summary of recent toxicological and epidemiological studies of $Hg^0$, predominantly as a result of occupational exposure, is presented in Table 7.

## 5.1 Review and Identification of Key Studies for Determination of a REL for $Hg^0$

### *5.1.1 Preliminary screening*

All references published in 1993 or later, relating to CNS, renal and immunological effects were identified through literature search (Table 7). Databases or web-resources consulted included the US EPA's Integrated Risk Information System (IRIS), the World Health Organization (WHO), the Registry of Toxic Effects of Chemical Substances (RTECS), Hazardous Substances Data Bank (HSDB), PubMed, TOXNET and Cambridge Scientific Abstracts. Also, researchers identified by ATSDR (1999) as involved in on-going research were directly contacted for details of any relevant studies they or their colleagues may be conducting.

The articles identified through the literature collection were pre-screened to identify which articles should undergo further critical review. Completed pre-screening forms for a total of 40 articles are presented in Appendix A; a list of other references considered but not screened is included as Appendix B. Pre-screening criteria are evident from forms included in Appendix A. Based on this pre-screening, 27 studies were identified for further critical review.

### *5.1.2 Critical evaluation*

The 27 articles identified through pre-screening as being potentially relevant in the development of a REL were submitted to further critical review to identify potential key studies for establishment of a REL for $Hg^0$. In addition, the 6 primary papers cited by the US EPA to develop and support its current RfC were evaluated according to the same critical review criteria. The completed critical evaluation forms for all 33 studies are presented in Appendix C.

The REL to be derived herein is analogous to US EPA's reference air concentration (RfC), which is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (US EPA, 2004). The inhalation REL is based on the assumption that thresholds exist for certain toxic effects. As such, in establishing a REL it is important to choose a key study that considers the most sensitive species (where adequate human data do not exist), the most sensitive gender and the most sensitive endpoint. All studies examined evaluated human subjects, except one. The studies related to humans all addressed occupational exposure that included predominantly healthy adult men. Based on the information available, it was not possible to address the influence of gender in choosing the principal study.

The critical review identified a total of 11 occupational studies that were considered potentially relevant in establishing or supporting the development of a REL. Studies were identified for each of CNS effects, renal effects and immunological effects. For each relevant article, information

concerning the toxic effect, effect level established by the study (i.e. LOAEL[1], NOAEL[2]), and exposure parameters are summarized in Table 8.

## 5.2 CNS Effects of $Hg^0$

Reported effects of chronic exposure on the central nervous system (CNS), occurring at doses ranging from 0.0007 to 0.945 mg/m$^3$, include: impairment of tests on neurobehaviour, intelligence and memory; increased aggression; tremors; difficulty with heel-to-toe gait; poor attention; bad temper; numbness; blurred vision; slow mental response; and memory disturbances (ATSDR, 1999; WHO, 2000, 2003). Chronic exposure in children has been reported to cause neurodevelopmental and neurobehavioural effects, such as decreased motor abilities and language skills, agitation, apathy and withdrawn moods, loss of social skills and other personality changes (Ozuah, 2001).

Based on the quantity and quality of information reported for each study in Table 8, a key study upon which to base a REL for CNS effects was identified as that of Ngim et al. (1992). Problems with the other studies are summarized as follows:

> Piikivi and Hanninen (1989) investigated 60 chloralkali workers(UHg = 84.1 nmol Hg/L or16.9 μg/L; equivalent Air-Hg concentration = 26 μg/m$^3$ (conversion after Tsuji et al., 2003) relative to 60 controls. That study suggested a NOAEL for psychological performance and subjectively reported symptoms. However, the study of Ngim et al. (1992) identified a lower exposure level (14 μg/m$^3$) that was effectively a LOAEL in that study. Also, results of studies of chloralkali workers may be confounded by concomitant exposure to chlorine gas (see Section 4.2)
>
> Fawer et al. (1983) investigated 26 Hg-exposed subjects (arithmetic average measured Air-Hg concentration = 26 μg/m$^3$) relative to 25 controls. The exposed group included 12 chloralkali workers. This study suggests a LOAEL for hand (intention) tremour of 26 μg/m$^3$. However, the study of Ngim et al. (1992) identified a lower exposure level (14 μg/m$^3$) that was a LOAEL in that study. Also, results of studies of chloralkali workers may be confounded by concomitant exposure to chlorine gas (see Section 4.2).
>
> Boogaard et al. (1996), in a study of gas production workers, reported that nerve conduction velocity, tremor, and psychological performance were not significantly altered in 18 high exposed subjects relative to 22 low exposed subjects and 19 controls. The mean exposure level for the low exposed group (average UHg = 4.1 μg/g creatinine; equivalent Air-Hg concentration = 2.3 μg/m$^3$) might suggest a NOAEL. However, numbers of subjects were small (n=22 in low exposure group; n=19 controls). Also, the description of exposure

[1]LOAEL: lowest observed adverse effect level; the lowest exposure level associated with statistically significant or biologically significant effects as compared to controls

[2]NOAEL: no observed adverse effect level; the hightest exposure level associated with no statistically significant or biologically significant effects as compared to controls

conditions is unclear and may have involved intermittent (periodic) rather than continuous chronic Hg exposure.

The study of Ngim et al (1992) was selected as the most reliable study upon which to base a REL to protect against CNS effects in the general population. Ngim et al. (1992) studied neuro-behavioural performance using a battery of tests in 98 Singapore dentists (60 males, 38 females) compared to 54 controls. These data were further analysed by Foo *et al.* (1993). The geometric mean Air-Hg concentration in the dental offices at the time of the study was 14 $\mu g/m^3$ (range 0.7 to 42 $\mu g/m^3$). Ngim et al. (1992) reported diminished performance in a variety of neuro-behavioural tests among dentists relative to controls.

Despite impaired neurobehavioural performance, Ngim et al. (1992) noted no significant difference between dentists and controls in a standardized composite intelligence score (based on 4 tests of intelligence; termed Z scores by the authors). Other studies involving dentists and dental workers (Shapiro *et al.* (1982) and Uzzell and Oler (1986)) have also reported no apparent impact on general intelligence, as assessed by the Weschler Adult Intelligence Scale. However, in a further analysis of the same Z scores, Foo et al. (1993) observed a dose/duration dependent progressive deterioration among exposed subjects in composite intelligence score with increasing measures of cumulative Hg dose.

Ngim *et al.* (1992) also found the Hg exposed group to have a more aggressive mood than controls, and a dose/duration dependent increase in aggressive mood with increasing Hg exposure. This is generally consistent with the findings in other groups of dental professionals by Gonzalez-Ramirez *et al.* (1995) (dose-dependent associations between UHg levels and anger and confusion, as well as with self reported symptoms of headache, emotional problems and comprehension), Echeverria *et al.* (1995) (dose-dependent associations of UHg levels with tension, fatigue, confusion, lack of vigour, and depression, as well as with symptoms related to emotion and concentration), Shapiro *et al.* (1982) and Uzzell and Oler (1986) (heightened distress).

One weakness occasionally cited with respect to the study of Ngim et al. (1992) was a possible deficiency in the amount of $Hg^0$ exposure monitoring conducted to quantify exposure. The concentration of mercury in air was measured for only one day for the majority of the participants and this single measurement formed the basis of exposure quantification. However, this same weakness is also apparent in a variety of other studies investigating $Hg^0$ exposure and CNS impairment, including Fawer et al. (1983).

### *5.2.1 Occupational Studies of Echeverria and colleagues*

Since the mid 1990s, Echeverria and colleagues have focussed their research on the associations between low level $Hg^0$ exposure (predominantly in dentists and dental assistants) and sub-clinical neuro-behavioural and psychological effects as measured by an extensive and objective test battery. These studies include:

- Echeverria et al. 1995. Behavioral effects of low-level exposure of Hg0 among dentists. Neurotoxicol Teratol., 17(2):161-168.
- Gonzalez-Ramirez et al., 1995. Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans: II. urinary mercury, porphyrins and neurobehavioural changes of dental workers in Monterrey, Mexico. J. Pharmacol. Exper. Therap., 272(1): 264-274.
- Bittner et al., 1998. Behavioral effects of low-level exposure to Hg- among dental professionals: a cross-study evaluation of psychomotor effects. Neurotoxicol. Teratol., 20(4): 429-439.
- Echeverria et al. 1998. Neurobehavioral effects from exposure to dental amalgam Hg0: new distinctions between recent exposure and Hg body burden. FASEB, 12: 971-980.
- Heyer et al., 2004. Chronic low-level mercury exposure, BDNF polymorphism, and associations with self-reported symptoms and mood. Toxicol Sci. 2004 Oct;81(2):354-63.
- Woods et al., 2005. The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. Toxicol Appl Pharmacol, 206:113 – 120.
- Echeverria et al., 2005. Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. Neurotoxicol Teratol, 27: 781 – 796
- Echeverria et al., 2006. The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans. Neurotoxicol Teratol, 28:39 – 48

These studies have been largely omitted from the evaluation of toxic effects posed by occupational $Hg^0$ exposure. This relates, in part, to the very recent publication of some of these studies. However, in other cases, the results appear to have been (incorrectly) marginalised as a component of the debate surrounding the potential toxicity of dental amalgam (WHO, 2003; ATSDR, 1999, for example).

Echeverria et al. (1995) evaluated neurobehavioral performance in 19 dentists with UHg concentrations in excess of 20 μg Hg/L (mean = 36.4 ± 20.0 μg Hg/L), relative to 20 dentists with UHg levels <0.5 μg Hg/L. Overall poorer performance among Hg-exposed dentists in cognitive and motor function tests was reported, based on pooled or composite test scores. A statistically-significant dose-dependent increase in impairment of verbal skill was also reported. They also observed dose-dependent associations of urine Hg levels with tension, fatigue, confusion, lack of vigour, and depression, as well as with symptoms related to emotion and concentration. A positive dose-effect association was observed with UHg concentration, with impairment increasing with increasing urine Hg concentration.

Gonzalez-Ramirez *et al.* (1995) reported deficits in tests of attention and perception in a group of 10 dental technicians (average UHg level of 29.7 ± 6.7 μg/L) and 5 dentists (average UHg level of 19.8 ± 7.2 μg/L), relative to 13 controls with an average UHg concentration of 3.00 ± 0.62 μg/L. Statistically-significant, dose-dependent detriments were reported in a variety of neurobehavioral tests, consistent with Echeveria et al. (1995), Ngim et al. (1992), amongst others. Gonzalez-Ramirez

*et al.* (1995) reported improved performance among Hg- exposed subjects in a test of coordination (one hole pin test). However, occupational requirements and/or practice of fine motor skill in the exposed group relative to the controls (non-dental personnel) may explain this observation.

Bittner et al. (1998) conducted a meta-analysis to evaluate the sensitivities of five psychomotor tasks previously used to assess preclinical effects of low-level $Hg^0$ exposure (urinary $\leq$55 µg Hg/L urine). Subject populations from six studies conducted over a 6 year period were pooled for a total subject population of 230. No comparable referent (control) group was included. Tests included two tests of hand steadiness, finger tapping, simple reaction time and hand tremor. A significant association ($p << 0.0001$) was observed with measured Hg exposure (as represented by UHg levels). A detrimental but non-statistically significant ($p = 0.17$) association was also observed for finger tapping.

Echeverria et al. (1998) evaluated potential CNS toxicity in 34 practising dentists and 15 dental assistants with UHg < 4 µg Hg/L urine. No control group was included for comparison. UHg was significantly associated with work-related factors as well as dental amalgam load in the teeth of study participants, suggesting that occupational and non-occupational $Hg^0$ exposures could not be distinguished in the study group. Symptoms and psychomotor performance significantly influenced by Hg exposure were finger tapping, hand steadiness and two measures of visual processing and attention. Measures of various aspects of mood (tension, anger, fatigue and confusion) were also significantly associated with UHg levels. Echeverria et al. (1998) also reported various significant associations of symptoms, psychomotor performance and mood with UHg measured after chelation therapy. Post-chelation UHg was considered a measure of Hg body burden associated with long-term chronic Hg exposure, as opposed to recent occupational or background exposure.

More recently, Heyer et al. (2004) and Echeverria et al. (2005) investigated associations between CNS effects and Hg exposure (as measured by UHg concentration) in a group of 193 male dentists and 233 female dental assistants in Washington state. No control group was evaluated for comparison. Mean UHg concentrations (3.32 ± 4.87 µg/L in dentists; 1.98 ± 2.29 µg/L in dental assistants) were among the lowest reported in the occupational toxicology literature for a group exposed occupationally to $Hg^0$, and is similar to UHg levels reported in urine for the general population.

Heyer et al. (2004) reported a variety of associations between increasing UHg levels and increases in various self-reported symptoms and measures of mood. Using an objective battery of tests, Echeverria et al. (2005) identified a variety of cognitive and psychomotor detriments as having a dose-dependent association with UHg concentrations, with detriments generally increasing as UHg concentration increased. Also, the sub-clinical severity of hand steadiness had a strong, statistically significant, linear relationship with UHg concentration (log-log scales) in both dentists and dental assistants. Statistical analysis could not define a threshold urinary concentration for the onset of declining hand steadiness.

Other investigations of this group have examined the potential for genetic predisposition to Hg toxicity, which is discussed later in this document.

*Discussion*

The investigations of Echeverria and colleagues are the first to broadly apply a battery of tests to investigate associations between Hg exposure and potential impairment on cognitive, neuromotor and psycho-behavioral function. The test batteries used by this group appear to have complied with the WHO neuro-behavioral core test battery. The results have proven consistent and reproducible, and relate to an occupational group without concomitant exposure to $Hg^0$ and chlorine gas (as in the case of chloralkali workers). Currently, data suggest that a detrimental impact of Hg exposure (as measured by UHg) is evident with no apparent threshold.

The results reported by this group are consistent with numerous previous evaluations of impaired cognitive and neurological function in association with increasing $Hg^0$ exposure, but extend the observed associations between CNS effects and Hg exposure to much lower exposure levels. The primary advances relate to the development and application of an objective test battery permitting reproducibility, and the evaluation of subjects with exposures < 25 ug Hg/L urine, greatly extending the potential for dose-response evaluation in the low dose range.

Currently, from the work of Echeverria and colleagues, it would appear that the intention tremor reported by Fawer et al. (1983) and various other authors decreases in severity as chronic Hg exposure levels decline below 25 ug/$m^3$ (25 ug/L urine) but no true threshold for extremity steadiness is evident. The effect becomes increasingly subtle (i.e., more sub-clinical) as exposure decreases, but a dose-response association appears evident, possibly down to background (non-occupational) exposure levels.

However, the more recent studies of this research group generally do not include control subjects with no occupational exposure to Hg. As a result, effects and trends observed in the subject populations cannot be adequately interpreted relative to non-occupationally exposed populations. Until such time as adequate controls are evaluated in a comparable manner as dental professionals, it is not possible to determine if the low exposure impacts reported in dental professionals by these researchers can be extrapolated to the general public.

## 5.3 Renal Effects of $Hg^0$

$Hg^0$ exposures have been reported to elicit the nephrotic syndrome, which consists of excessive loss of protein in the urine and oedema with albumin and hyaline casts in the urine (WHO, 2000). Urinary dysfunction has been marked by increased urinary excretion of Tamm-Horsfall glycoprotein, and tubular antigens, decreases in urinary pH and decreased excretion of glycoaminoglycans, prostaglandin E2 and F2$\alpha$ and thromboxane B2 (ATSDR, 1999). Glomerular changes resulting from Hg exposure have predominantly been reported as increases in high-molecular weight proteinuria (Buchet et al., 1980; Tubbs et al., 1982; Stonard et al., 1983). Renal tubular changes in workers exposed to Hg include increased urinary excretion of N-acetyl-beta-D-glucosaminidase (NAG), $\beta$-galactosidase, and retinol binding protein (Rosenman et al., 1986; Barregard et al., 1988; Langworth et al., 1992; Ellingsen et al., 2000; Bazzi et al., 2002).

Based on the quantity and quality of information reported for each study in Table 8, no adequate key study upon which to base a REL for renal effects could be identified. Problems with the other studies are summarized as follows:

Boogaard et al. (1996) investigated gas production workers and reported that NAG levels were statistically significantly elevated in the urine of a high exposed group (average UHg = 23.7 μg/g creatinine) relative to the low exposed group (average UHg = 4.1 μg/g creatinine) and controls. The low exposed group would suggest a NOAEL. However, numbers of subjects were small (n=22 in low exposure group; n=18 in high exposure group; n=19 controls). Also, the description of exposure conditions is unclear and may involve intermittent (periodic) rather than continuous chronic Hg exposure.

Cardenas et al. (1993) reported a variety of markers for functional renal toxicity, cytotoxicity and biochemical changes in association with Hg exposure in chloralkali workers relative to unexposed controls. Stratification of results among three exposure groups (controls: UHg<5 μg/g creatinine; moderate: 5 μg/g creatinine ≤ UHg ≤ 50 μg/g creatinine; high: UHg > 50 μg/g creatinine) suggests a LOAEL based on the moderately exposed group, for alteration of NAG levels (amongst other markers). However, the precise exposure levels for each subgroup (mean, standard deviation) were not reported; only an overall mean UHg for all exposed subjects was reported (mean UHg = 31.9 μg/g creatinine). Also, results of studies of chloralkali workers may be confounded by concomitant exposure to chlorine gas (see Section 4.2).

Ellingsen et al. (2000) reported urinary NAG levels to be statistically significantly higher in the Hg exposed group of chloralkali workers relative to controls. The apparent LOAEL exposure level was 5.9 nmol Hg/mmol creatinine in urine (10.5 μg Hg/g creatinine, equivalent). The equivalent 8 hour TWA Air-Hg concentration associated with this UHg concentration is 10.2 μg $Hg/m^3$ air (conversion after Tsuji et al., 2003). Reported effects included increased U-NAG levels, suggestive of damage to renal proximal tubule cells mediated by neutrophils. Also, urinary NAG concentration was positively correlated with UHg concentration, and with a measure of cumulative (multi-year) Hg exposure. Although results of CNS studies of chloralkali workers may be confounded by concomitant exposure to chlorine gas (see Section 4.2), the same cannot be confirmed for renal effects, since the kidney is the main organ of deposition for both $Hg^0$ and $HgCl_2$ (ATSDR, 1999). However, additional data are required to substantiate a consistent, reproducible effect on urinary NAG levels at UHg levels below 25 μg/g creatinine (< 25 μg $Hg/m^3$) (discussed below). As a result, reliance on the study of Ellingsen et al. (2000) as a basis of a REL for $Hg^0$ is premature at this time.

### *5.3.1 Urinary NAG Levels as a Measure of Renal Toxicity of $Hg^0$ Exposure*

NAG is an enzyme located mainly in the lysosomes of proximal tubular cells and its increased activity in urine is known to be associated with ailments and chemical exposures which impair renal function (Barregard *et al.*, 1988). Increases in NAG as a result of renal toxicity have also been

observed with heavy metals such as cadmium, lead, iron and uranium (Khalil-Manesh et al., 1992; Jin et al., 1999; deBurbure et al., 2003; Koliakos et al., 2003) as well as some organic compounds, such as trichloroethylene, which results in similar effects on NAG levels (Mensing et al., 2002).

There is a growing database concerning the relationship between urinary NAG levels and $Hg^0$ exposure, as quantified by UHg levels in exposed individuals. A number of studies have concluded that monitoring of NAG levels is a sensitive tool in the early detection of renal toxicity (Price, 1979; 1982; Stonard et al. 1983; Goyer, 1990; Bazzi et al., 2002; deBurbure et al., 2003). Several studies, many of them recent, have demonstrated a dose-dependent relationship of U-NAG with Hg exposure (and often with U-Hg). Elevated urinary NAG levels occurred with UHg levels of 100–250 μg/L in a study population of mixed ethnic background (Rosenman et al., 1986), with UHg levels of 35 μg/g creatinine in chloralkali workers (Barregard et al., 1988), with UHg levels >25 μg/g creatinine in chloralkali workers (Langworth et al., 1992), and with UHg levels >50 μg/g creatinine in another group of chloralkali workers (Cardenas et al., 1993). Similarly, a more recent study by Kobal et al. (2000) noted an increase in NAG levels associated with mean UHg levels of 92.3 μg/g creatinine in exposed miners. An examination of thermometer plant workers by Himeno et al. (1986) concluded that a threshold for Hg-NAG dose-response relationship existed at 79.5 μg/g creatinine. Up until the study of Ellingsen et al. (2000), the general consensus had been that the threshold for potential renal effects as noted by increasing NAG levels was related to a UHg level around 35 μg/g creatinine (~50 μg/L), which was subsequently used to derive exposure limits for inhalation exposure to inorganic Hg (WHO, 1980; Barregard et al. 1988; Boogaard et al., 1996).

There is no information available concerning the relationship of urinary NAG levels and the severity of the renal effect(s) in relation to $Hg^0$ exposure. However, the effects are considered reversible upon cessation of exposure. Research concerning NAG levels in the context of Hg exposure has focussed on identifying relationships between dose and increasing NAG, as well as urinary Hg and NAG activity. While there is sufficient evidence in the reviewed studies to indicate a clear relationship between UHg levels and $Hg^0$ exposure, there is variability in what UHg level causes increases in NAG levels.

Until the study of Ellingsen et al. (2000), the general consensus had been that the threshold for potential renal effects as noted by increasing NAG levels was related to a UHg level around 35 μg/g creatinine (Roels et al., 1999), which was used as the basis for the biological exposure index (i.e., acceptable occupational urinary Hg concentration) resulting from inhalation exposure to $Hg^0$ (WHO, 1980; Barregard et al. 1988; Boogaard et al., 1996). The study of Ellingsen et al. (2000) has challenged this position, as they observed elevated NAG levels at lower UHg levels than previously recognized (i.e., at $\geq$10 μg Hg/g creatinine in urine).

There are also a number of studies in the available literature indicating that there is no relationship between exposure to Hg and increases in NAG levels. NAG levels were reported to be unaffected by Hg exposure in chloralkali workers with UHg levels of 15 μg/g creatinine (Piikivi and Ruokonen 1989). A number of more recent studies have also concluded that no relationship existed between Hg exposure and elevated NAG levels with reported UHg levels of up to 24 μg/g creatinine (Sanborgh-Englund et al., 1996; Frumkin et al., 2001; Ishihara, 2000; DeBurbure et al., 2003).

However, it should be noted that the UHg levels of all the studies exhibiting no increase in NAG levels were below the previously identified threshold level for renal effects of 35 μg/g creatinine (WHO, 1980; Barregard et al. 1988; Boogaard et al., 1996).

*5.3.1.1 Discussion of NAG as a biomarker for $Hg^0$ renal toxicity*

Eight of 13 recent studies identified statistically significant increases in NAG levels with Hg exposure (as represented by UHg concentration), either in the entire exposure group or within a subgroup with (relatively) higher exposure. NAG in urine is a biomarker for damage to the renal proximal tubules. Therefore, there is a weight of evidence supporting NAG levels in urine as a dose-dependant marker for renal damage caused by Hg vapour exposure. However, there is a lack of data directly correlating NAG levels to the extent of renal damage or effects. Elevated NAG levels have been clearly associated with toxicity in the renal tubules (ATSDR, 1999); however, there are no studies available that have examined the severity of the observed toxicity in relation to NAG levels.

There is a growing database concerning the relationship between NAG levels and UHg levels in exposed individuals. The weight of evidence suggests that a threshold may exist for a UHg level below which there is no increase (or at least no consistent increase) in NAG levels. The available studies are contradictory on this issue. Some studies suggest a threshold of perhaps 100 μg/g creatinine; others suggest a possible lowest effect level of perhaps 35 μg/g creatinine (approximately equivalent to an ambient air concentration of 25 $\mu g/m^3$) (Roels et al. 1999). Ellingson et al. (2000) is the first study to clearly observe elevated levels of urinary NAG at levels of UHg as low as 10 μg/g creatinine.

U-NAG may be the most sensitive adverse toxicological response to Hg vapour exposure in human studies. The relationship of U-NAG with Hg exposure (predominantly as U-Hg) is dose-dependent, and has proven to be reproducible (8 of 13 studies). Studies of the effect of $Hg^0$ exposure on urinary NAG levels appear to provide the lowest LOAEL value from which to derive a precaution-based REL for $Hg^0$. The study of Ellingsen et al. (2000) provides the lowest reported LOAEL of all effects and key studies identified upon which a REL for $Hg^0$ might be established. However, based on an overall weight of evidence, extensive and definitive epidemiological data are lacking to demonstrate a consistent, reproducible effect at UHg levels below 25 μg/g creatinine (< 25 $\mu g\ Hg/m^3$).

## 5.4 Immunological Effects of $Hg^0$

Effects are also observed on the immune system. Exposure to concentrations of 0.024 – 0.09 $mg/m^3$ Hg for periods of less than ten and up to 31 years caused stimulation of T-lymphocytes in peripheral blood without effect on NK-cell count, indicative of an autoimmune response (ATSDR, 1999). Other effects observed at unspecified doses have included granular deposition of IgG and complement C3 in the glomeruli of the kidneys, increased antiglomerular basement membrane antibodies, reduced neutrophil function, elevated anti-nuclear antibodies, abnormally high anti-DNA antibody titre as well as increases in IgA and IgM (ATSDR, 1999).

### *5.4.1 Key studies of immunological effects*

Based on the quantity and quality of information reported for each immunological study identified in Table 8, a key study upon which to base a REL for immunological effects could not be identified. Problems with each study are summarized as follows:

Moszczynski et al. (1995) reported significantly increased counts of T-cells (CD3+), T-helper (CD4+), and T-suppressor (CD8+) cells in exposed chloralkali workers. The TWA for Hg in air ranged from 0.024-0.09 mg/m$^3$ (median 0.036 mg/m$^3$), with a weighted mean Hg air level was 0.028 mg/m$^3$. Lesser increases were observed in workers exposed for less than 10 years relative to workers exposed for greater than 10 years. A positive correlation was found between T-helper cell (CD4+) count and exposure duration. No significant differences in the absolute count of CD16+ cells were observed between exposed and control subjects; however, a fall in the percentage on Natural Killer cells (NK, or CD16+) was observed in exposed workers. It is not clear that the changes observed represent a significant adverse effect. Also, the results of studies of chloralkali workers may be confounded by concomitant exposure to chlorine gas, owing to likely differing distributions between blood plasma and erythrocytes, and differing organ and tissue distributions (see Section 4.2).

Park et al. (2000) observed significant decreases in total CD4+ and CD4+45RA+ T lymphocytes in exposed fluorescent lamp factory workers relative to controls. The reported average UHg concentration (44.8 μg/L) was not generally consistent with the reported Air-Hg concentration (4.1 μg/m$^3$); the expected Air-Hg concentration generally anticipated to correspond to the reported UHg value would be 5 to 10 times greater. The number of CD57+CD16+ NK cells was observed to be inversely related to HgU levels. No Hg exposure measurement was made for concurrent controls; the authors assumed a value for controls (as UHg concentration) derived from secondary, unrelated reference published in 1990. It is not clear that the changes observed represent a significant adverse effect.

Perlingeiro and Querioz (1995) reported significant impairment of chemotaxis and nitroblue tetrazolium dye reduction in blood samples of exposed mercury production/recovery workers relative to controls during the first of two evaluations, and the level of neutrophil impairment did not return to normal after 6-months (second evaluation) of reduced exposure. Hg exposure was determined by urinalysis, with UHg levels ranging from 1.0 to 97.4 μg/g creatinine, with an apparent average concentration in exposed workers of 24 μg/g creatinine. No Hg measurements were conducted for the control cohort. The average duration of exposure was only 8-months (range: 0.5-46 months), and it is not clear how many workers experienced acute versus short-term versus intermittent exposures to Hg. Therefore, chronic exposure is questionable.

The study of Queiroz et al. (1994) was an extension of that of Perlingeiro and Querioz (1995), investigating the same exposed and control cohorts. Significantly increased levels of IgG, IgA and IgM were observed in exposed workers relative to controls, but no correlation between exposure duration and immunological levels was observed. As with Perlingeiro and Querioz (1995), mean HgU was about 24 μg/g creatinine, with the majority of subjects below 50 μg/g creatinine. The average duration of exposure was only 8-months (range: 0.5-46 months), and it is not clear how many workers experienced acute versus short-term versus intermittent exposures to Hg. Therefore, chronic exposure is questionable. No Hg measurements were conducted for the control cohort.

## 5.5 Fetal Effects of Hg

As $Hg^0$ is biologically mobile and can readily cross the placenta (WHO, 2003; also see Section 3.1, above), potential fetal effects are a concern in association with the inhalation of $Hg^0$ by pregnant women (WHO, 1991; Drasch et al., 1994; Yang et al., 1997). The uptake and distribution of Hg in the fetus following maternal exposure to $Hg^0$ has been extensively reviewed (ATSDR, 1999; WHO, 2003). No hepatic or renal effects have been noted as a result of *in utero* exposure despite the fact that the liver and kidney accumulate the highest levels of Hg in the fetus (Drasch et al., 1994; Morgan et al., 2002; Yoshida, 2002; Yoshida et al., 2002).

A number of animal studies have demonstrated developmental neurological effects in association with gestational animals following maternal $Hg^0$ exposure. Studies in rats have found that gestational exposure to Hg vapour affected growth-related signal transduction in neonatal brains (Soderstrom et al., 1995). Behavioral effects in animal studies have been noted as symptomatic indicators of fetal exposures (Fredriksson et al., 1992). In general, fetal exposures to Hg vapour have been noted to cause delayed neurological development in exposed animals (Danielsson et al., 1993; Fredriksson et al., 1996; Newland et al., 1996).

A number of recent studies have examined the effects due to *in utero* exposure to Hg and have pointed to potentially irreversible neurological effects as the key toxicity endpoint (Ramirez et al., 2003). This result points to the sensitivity of the developing CNS to exposures to Hg, with one author attributing this sensitivity to Hg's slow elimination from these tissues (Yoshida et al., 1999). However, while the CNS is a sensitive target for Hg toxicity in the developing fetus, a number of studies have noted that there are several protective mechanisms present (e.g., metallothionein binding), which play a role in Hg availability in these tissues (Aschner et al., 1997; Warfvinge, 2000; Pamphlett and Kum-Jew, 2001; Yoshida et al., 2002; Yoshida et al., 2005).

In a study by Newland et al. (1996), a total of six (3/dose) pregnant squirrel monkeys were exposed to 0.5 or 1.0 $mg/m^3$ of Hg vapour for 4 or 7 hr/day, 5 days/week during the last two-thirds or more of gestation. The authors reported that the maternal exposures resulted in daily doses (calculated assuming 80% absorption via inhalation) ranging from 21-38 μg Hg in the 0.5 mg $Hg^0/m^3$ group and from 42-62 μg Hg in the 1.0 mg $Hg^0/m^3$ group. The resulting median concentrations of Hg in the maternal blood ranged from 0.025 up to 0.18 μg/L during the exposure period. No determination of fetal (*in utero*) exposure was made in the study. The authors noted alterations in the offspring in three aspects of behaviour maintained by a concurrent schedule of reinforcement: steady-state performance, transitions to new schedule parameters and lever press durations. No differences in birth weight, weight gain or body weight were observed in the offspring as a result of *in utero* exposure.

Fredriksson et al. (1992) exposed pregnant rats at a concentration of 0.05 $mg/m^3$ on gestational days 11 to 17 for 1 hour per day (low dose) or for 4 hours per day (high dose), and tests for spontaneous motor activity were performed on the offspring. Offspring of the high dose group showed a marked increase in locomotion and total activity and a decrease for rearing at 2 months of age, and showed a marked hypoactivity in all three variables at 4 months of age. Offspring of rats in the low dose

group showed no significant differences from controls at 2 months but displayed the same effects and trends observed in the high dose group at 2 months of age.

Furthering the investigation of Fredriksson et al. (1992), Danielsson et al. (1993) examined fetal effects of exposure in three groups of 12 Sprague-Dawley rats exposed via inhalation to 1.8 mg/$m^3$ of elemental Hg vapour on gestation days 11–14 and 17–20 for one hour per day ("low dose") or three hours per day ("high dose"). At postpartum day 3, each litter was reduced to 4 male and 4 female offspring. The authors reported no significant differences between the Hg-treated offspring and the controls for surface righting, negative geotaxis, and tooth eruption. Behavioural tests (e.g., spontaneous motor activity, spatial learning, etc.) suggested that exposure to Hg *in utero* resulted in adverse effects characterized by hypoactivity at 3 months or age but hyperactivity at 14 months. Decreased learning and decreased adaptation skills were also noted. The authors noted that the effects observed were similar to the behavioural changes noted with exposure to methyl Hg.

In a subsequent study by this research group (Fredriksson et al., 1996), at 4 to 5 months of age, rats exposed *in urtero* showed significant hyperactivity in spontaneous motor activity tests of locomotion, rearing, and total activity, in association with maternal exposure to 1.8 mg/$m^3$ for 1.5 hours/day during gestation days 14–19.

In a recent study published by Yoshida et al. (2005), neurobehavioural effects of prenatal exposure were examined with respect to the potential protective effect of metallothionein (MT). Pregnant mice of MT-null and wildtype strain were repeatedly exposed to elemental Hg vapour at concentrations of 0.5 and 0.56 mg/$m^3$, respectively, for 6 hr/day from gestational day 1 through 18. Hg concentrations in the brain and kidney in the mice exposed *in utero* were found to be significantly higher in the exposed groups (MT-null and wildtype) than in the controls. In the brain, Hg concentrations in the exposed males were not significantly different between the two strains, but the exposed MT-null females had significantly higher levels of Hg compared with the wildtype. The authors reported that a histological examination did not reveal any abnormalities in the nerve tissues of the exposed mice regardless of strain or sex of the offspring. Behavioural effects evaluated in the study noted that Hg-exposed MT-null mice exhibited a significant decrease in total locomotor activity in males, and a learning disability in the passive avoidance response and a retarded acquisition in the Morris water maze in females as compared with the controls. The authors concluded that MT may play a protective role for neurological effects associated with *in utero* exposure with this protective effect being more pronounced in females by impairing Hg uptake into the brain.

Another recent study examined the disposition and toxicity of inhaled elemental Hg vapour in rats and the potential adverse effects on reproductive outcome (Morgan et al., 2002). Rats were exposed to 0, 1, 2, 4, or 8 mg Hg/$m^3$ for 2 hr/day from gestation day 6 through 15. Maternal toxicity was noted in those rats exposed to 4 and 8 mg Hg/$m^3$, which was characterized as a concentration-related decrease in body weight gain and mild nephrotoxicity. The accumulation of Hg in fetuses was found to be dose-dependent, however no statistically significant effects on fetal brain weights or on fetal body weights were noted even with fetal Hg concentrations being noted to reach a mean of 108.8 ng Hg/fetus (whole body) on gestational day 10 (the only day on which whole body burden was

examined) and 1.93 ng/brain by gestational day 15. The authors also noted a dose-related increase in levels of Hg in the fetal brain. While no effects were noted in the offspring as a result of *in utero* exposure, a significant increase in the number of resorptions was noted with maternal exposure to 8 mg Hg/$m^3$. In addition, postnatal litter size and body weights of neonates associated with maternal exposure to 8 mg Hg/$m^3$ were reported to be significantly less when compared with controls. However, direct maternal toxicity was reported at this exposure level, confounding the attribution of this observation to Hg exposure, per se.

While several animal studies have clearly noted neurological effects, fewer studies were identified that have characterized fetal effects in humans associated with maternal exposure to inhaled elemental Hg. There are several reports available in the literature detailing maternal exposures to Hg vapour of unknown concentrations that have described no adverse effects in the newborn child as a result of *in utero* exposures (Brodsky et al., 1985; Melkonian and Baker, 1988; Ericson and Kallen, 1989; Thorp et al., 1992). The difficulty in making any interpretations of the potential for fetal effects based on these reports is the lack of exposure data.

While the human studies described above did not identify a link between Hg exposure and pregnancy outcome (e.g., stillbirths or miscarriages) there are others which suggest that the opposite is true. In an occupational study conducted by Elghany et al. (1997) the effects of occupational exposure to inorganic Hg on pregnancy were investigated among 46 exposed women workers: controls were 19 women working in non-production areas of the same factory. The study reported a higher frequency of adverse reproductive outcomes, especially congenital anomalies, among the women exposed to inorganic Hg levels at, or substantially lower than 0.6 mg/$m^3$. However, the study reported that there were no significant differences in the stillbirth or miscarriage rates between the two groups of women, with the authors noting that the overall fetal death was similar to national levels for the same period.

A recent study examined the presence and levels of total Hg in cord blood and meconium as an indicator of prenatal exposure and the potential to cause neurodevelopmental effects (examined using cognitive adaptive tests and clinical linguistic auditory milestone scale – CATS/CLAMS) (Ramirez et al., 2003). The authors did not provide details concerning the source of the exposures to Hg (both elemental and methyl Hg) in the study, but noted that there was likely some exposure to methyl Hg via the diet, due to the consumption of fish. The study reported that Hg levels in hair and cord blood were negatively correlated with CATS/CLAMS results in both the control and exposed groups at two years of age. However, those exposed were also found to be negatively correlated with documented indicators of Hg presence at birth (presence of Hg in the meconium) and therefore, the authors suggested that prenatal exposure and not necessarily current exposure to Hg in children (e.g., birth to 2 years of age) were the cause of the observed neurodevelopmental effects. While this study suggests that *in utero* exposure may result in neurological effects, these results should be interpreted with caution, as the authors state that they did not control for confounding variables, such as concomitant exposure to other pollutants and nutritional deficiencies.

### *5.5.1 Summary and conclusions: fetal effects*

Evidence suggests that the distribution of Hg in fetal tissues following *in utero* exposure results in the highest levels of Hg in the kidneys and liver, as would be predicted based on observed effects in exposed workers (Drasch et al., 1994; Morgan et al., 2002; Yoshida, 2002; Yoshida et al., 2002). However, the CNS, more specifically, the developing fetal brain, would appear to be a more sensitive target for *in utero* exposure, with a general absence of observed renal toxicity (Danielsson et al., 1993; Fredriksson et al., 1996; Newland et al., 1996; ATSDR, 1999; Warfvinge, 2000; Warfvinge and Bruun, 2000).

Available dose-response data related to fetal neurotoxicity is limited. A number of studies have identified dose-dependent increases in brain-Hg concentrations, without associated effects. Available animal data suggest that maternal exposure to elemental Hg of 0.5 $mg/m^3$ may result in adverse neurological effects in the offspring. Available dose-response data based on fetal tissue measurements during exposure was limited to a single study (Morgan et al., 2002) that reported a no-effect-level of 108.5 ng Hg/fetus (whole body) in rats.

Evidence from animal studies suggests that the CNS is sensitive to prenatal Hg exposure. However, clear dose-response data in relation to inhalation exposure to elemental Hg are lacking. In addition, available data relate to Hg air concentrations of 2 to 3 orders of magnitude greater than that generally encountered in the non-occupational environment. Quality epidemiological data (good exposure data, control of confounding factors) is lacking concerning the potential for CNS effects in children with *in utero* exposure. Therefore, while there is evidence to demonstrate that fetal exposure does occur, and to suggest some potential for concern for neurobehavioral effects with fetal exposure following maternal inhalation exposure to $Hg^0$, data are lacking to quantitatively characterize any potential risks that may (or may not) exist.

## 5.6 Genetic Predisposition to Hg Renal Toxicity

A variety of studies in animals ((Aten et al. 1992; Druet et al. 1978; Hirszel et al. 1985; Hultman and Enestrom 1992; Matsuo et al. 1989; Michaelson et al. 1985; Pelletier et al. 1990; Pusey et al. 1990; Roman-Franco et al. 1978; van der Meide et al. 1993) (see reviews by Silbergeld et al., 2005; Nielson and Hultman, 2002; ATSDR, 1999) demonstrate the occurrence of autoimmune glomerulonephritis upon exposure to $Hg^0$ in genetically susceptible animals. Autoimmune glomerulonephritis results in observed proteinuria as a result of autoantibodies reacting with renal tissues. Some human evidence supports the existence of an immunologically-mediated renal impact, with deposition of IgG, immune complexes, and/or complement C3 along the glomerular basement membrane (Lindqvist et al. 1974; Tubbs et al. 1982). This evidence has been interpreted as evidence of a potential genetic predisposition to immunologically-mediated renal response to Hg exposure, although the existence of a genetic polymorphism coding for the requisite genetic susceptibility has not be reported.

Echeverria and colleagues (Echeverria et al., 2006, 2005; Woods et al., 2005; Heyer et al., 2004) have recently identified polymorphisms in genes encoding for brain-derived neurotrophic factor (BDNF). Various detriments in neuro-behavioural performance (Echeverria et al., 2006, 2005) and

self-reported symptoms and mood (Heyer et al. (2004) were associated with the presence of the BDNF polymorphism (frequency = ~25-35% in the population of study subjects (193 male dentists; 233 female dental assistants)), independent of Hg exposure level. The combined effects of the polymorphism and Hg exposure appeared to be additive.

The presence of a polymorphism for coproporphyrinogen oxidase (CPOX4; frequency = ~15% of subjects in Woods et al. (2005); ~25% of study subjects in Echeverria et al. (2006)) has also been observed and was associated with detriments in neurobehavioral response independent of Hg exposure. As with BDNF, the influence of the CPOX4 polymorphism and Hg exposure was additive.

### *5.6.1 Summary: genetic predisposition to $Hg^0$ toxicity*

Animal studies suggest autoimmune glomerular nephritis from $Hg^0$ exposure when genetic susceptibility exists. However, such susceptibility in the human population has not been identified nor the frequency of occurrence of a gene encoding such susceptibility reported.

A variety of recent studies by Echeverria and colleagues have identified two genes with polymorphisms, the presence of which are directly and independently associated with detriments in measures of neuro-behavioural performance. These detriments are also independent of, but additive to, the detriments associated with Hg exposure. These results would suggest that the presence of the identified genetic polymorphisms do not necessarily put persons at risk of enhanced toxic response to Hg exposure. Instead, the data might suggest that persons with these polymorphisms respond to Hg exposures in a manner similar to those with (normal) genes lacking the nucleotide substitutions, but from a diminished starting point with respect to neuro-behavioural performance.

Current data do not permit a quantitative analysis of the potential for, or frequency of, genetic predisposition to Hg toxicity in the general population. Those with this genetic predisposition would represent another sensitive subset of the population at particular risk to the effects of Hg vapour exposure; a predisposition that is not adequately addressed in the available studies of nephrotoxicity or immunotoxicity of $Hg^0$ exposure.

## 5.7 Carcinogenicity

The potential carcinogenicity of Hg has been extensively reviewed by the International Agency for Research on Cancer (IARC 1993) and by Boffetta *et al.* (1993). IARC (1993) concluded that metallic Hg and inorganic Hg compounds were not classifiable as to their carcinogenicity to humans (IARC Group 3). Confounding exposures to other potential carcinogens such as arsenic or radiation, no demonstrable dose-response associations in the limited data available, and no consistent types or sites of cancers, suggest that Hg vapour is not likely an occupational carcinogen. However, better epidemiologic and experimental evidence are needed to confirm that Hg is not an occupational carcinogen (Boffetta *et al.* 1993).

In the only study that examined the association between cancer incidence and the presence of amalgam dental fillings, Ryan *et al.* (1992) reported a significantly decreased risk of glioma (tumour of the supporting structure of nervous tissue) (sex and age-adjusted relative risk = 0.47; 95% confidence limits 0.25 to 0.91), although no linear trend with number of amalgams was evident.

From these reviews and studies, it was concluded that carcinogenicity is not a probable hazard associated with low level of $Hg^0$ exposure.

# 6 DEVELOPMENT OF THE REFERENCE EXPOSURE LEVEL FOR $Hg^0$

The key study identified herein for determination of a REL for $Hg^0$ was that of Ngim et al. (1992). From that study, a LOAEL for CNS effects was identified as 14 $\mu g/m^3$ (geometric mean reported by authors).

## 6.1 Correction of Occupation TWA Concentration for Continuous 24 hour Exposure

Exposure levels and units for key studies must be adjusted and/or extrapolated as necessary to provide a comparable 24 hour time-weighted average (TWA) air concentration, which is most relevant for exposures in the general, non-occupational population. Occupational 8 hour TWA airborne concentrations are routinely extrapolated to equivalent 24 hour exposure levels, for derivation of chronic duration RELs. This is often achieved by a simple adjustment whereby the occupational work week of 8 hours per day, 5 days per week is amortized to 24 hours per day, 7 days per week. However, Foo et al. (1993), in a follow-up analysis of the same study reported by Ngim et al. (1992), reported that the subject dentists worked Monday to Friday from 9 am to 5 pm and from 7 pm to 9 pm, and also on Saturdays from 9 am to noon. Assuming a 1 hour break each day for lunch, the weekly occupational exposure amounted to 48 hours out of a total 168 hours in a 7 day week.

The hourly inhalation rate of active (such as working) individuals is greater than persons at rest (see Allan and Richardson, 1998; US EPA, 1997b). As a result, the inhalation of a working (occupationally exposed) person during the regular 8 hour work day is greater than $1/3^{rd}$ of total daily inhalation (i.e., > 8/24 hrs). Adults actively involved in occupational activities inhale, on average, about 1.25 $m^3$/hour (US EPA, 1997). This equates to 60 $m^3$ of air inhaled per the 48 hour work week for the dentists investigated by Ngim et al. (1992). A typical adult not involved in occupational activities inhales on average 0.67 $m^3$/hr (HC, 2004; Allan and Richardson, 1998). This would equate to the inhalation of 80 $m^3$ of air during the 120 hour non-occupational period throughout the same 7 day period. Therefore, the total volume of air inhaled was 140 $m^3$ during a 7 day week. Based on the information above, the adjusted, equivalent continuous, time-weighted average exposure was determined to be 6 $\mu g/m^3$ (14 $\mu g/m^3$ X [60$m^3$/week ÷ 140 $m^3$/week]).

## 6.2 Uncertainty Factors (UFs) and Modifying Factor (MF)

### *6.2.1 Uncertainty factor for inter-species variability*

Key studies are often conducted on laboratory animals. In such cases, it may be impossible to determine if humans are more or less sensitive to exposure to the subject toxicant than the test animal species. As a result, it is customary to assume that humans are more sensitive than the test animals, and to apply an uncertainty factor of 10 for inter-species variability in toxicity.

However, the study of Ngim et al. (1992) investigated the CNS effects of $Hg^0$ exposure in human subjects. Therefore, no adjustment for inter-species variability in toxic response is necessary, and the UF for inter-species variability was set at a value of 1.

### *6.2.2 Uncertainty factor for inter-individual variability*

The study of Ngim et al. (1992), as with most other occupational studies, involved otherwise healthy human subjects. Also, the majority of subjects were male (60 males versus 38 females). Inter-individual (intra-species) variability in response to chemical exposures is known to exist, related to variability in toxic response, variability in uptake/retention/excretion, or both. Within the study of Ngim et al. (1992), men and women differed in a number of characteristics including average age (34 yrs versus 28 years), average personal amalgam load (9 versus 13 surfaces) and average duration of dental practice (106 versus 61 months). Such differences may also have introduced inter-individual variation in results. In cases where inter-individual variability is known, but can not be directly quantified, it is customary to apply an uncertainty factor of 10 in the derivation of reference exposure levels from studies of specific subsets of the general population.

Ngim et al. (1992) reported insufficient data and information to quantify directly the inter-individual variation in response to $Hg^0$ exposure in study subjects. Based on an extensive evaluation and review of other multiple lines of evidence (Appendix D), an uncertainty factor for inter-individual variability among occupational study participants of approximately 2 could be determined, encompassing variation in pharmacokinetics and toxicity of $Hg^0$. However, the data upon which this analysis could be conducted related almost exclusively to occupational exposure of adult males. The derived factor of 2 did not encompass gender differences, potential age-related differences (such as fetal toxicity), or susceptible sub-populations (such as genetic susceptibility to renal toxicity) in response to $Hg^0$ exposures. The potential for reduced absorption and toxicity of $HgCl_2$ in chloralkali workers also could not be quantified.

As discussed above, while the evidence is limited, there are sufficient data to demonstrate that gender differences in uptake, distribution and excretion do exist, and a data-derived uncertainty factor of 2 based on male subjects is not considered adequate to encompass that gender variability. In addition, identified sensitive populations (fetus, individuals with possible genetic predisposition to $Hg^0$ toxicity) preclude the application of an uncertainty factor of 2 for inter-

individual variability. Considering the evidence of gender differences, genetic predisposition, and potential effects following fetal exposure, a total uncertainty factor of 10 was determined to best address uncertainties in inter-individual variability and addressing sensitive subpopulations.

### *6.2.3 Uncertainty factor for adjustment from sub-chronic to chronic exposure*

Key studies are often limited to less-than-lifetime duration in animals, or to durations of less than 1 year in humans. In such cases, it is necessary to establish a REL at a level lower than the LOAEL/NOAEL in sub-chronic studies, to ensure that the REL reflects, based on available data and knowledge, an exposure level free from toxic effects during continuous, chronic duration exposure.

The average duration of exposure for subjects of the Ngim et al. (1992) study was 7.4 years (range: 0.7 to 24 years) which is considered herein to be chronic duration exposure (> 1 yr). Therefore, no adjustment from sub-chronic to chronic exposure duration was necessary, and the UF for this factor was set at a value of 1.

### *6.2.4 Uncertainty factor for adjustment from LOAEL to NOAEL*

Key studies often fail to identify a level of exposure (other than controls) at which no effects were observed within the study subjects. The lowest dose level at which effects were observed is identified as a LOAEL. In such cases, it is necessary to establish a REL at a level lower than the LOAEL, to ensure that the REL reflects, based on available data and knowledge, a level free from toxic effects.

The median $Hg^0$ airborne concentration of 14 $\mu g/m^3$ reported by Ngim et al. (1992) was interpreted to be a lowest-observed-adverse-effect-level (LOAEL), as no threshold for effects was reported for any component of the exposed subjects. Although the observed effects are subtle and non-clinical, they are still considered significant. Therefore, an uncertainty factor of 10 is appropriate to address the uncertainty with respect to the dose or exposure level associated with no observed adverse effects.

### *6.2.5 Modifying factors for consideration of database quality*

The number of toxicity studies is often very limited for chemicals. In many cases, toxicity studies have been conducted on only 1 or a few species, have investigated only one or a few toxic endpoints, or have evaluated the toxicity of a narrow range of exposure levels or doses. In such cases, an additional modifying factor (UF) is applied to reflect the limitations in the toxicological database, to increase the likelihood that a REL established on the basis of a measured endpoint will also protect against other, unmeasured toxic endpoints.

With respect to $Hg^0$ exposure, *in utero* fetal exposure is evident and detrimental effects have been noted in animal studies. However, no adequate human data exist, and effects observed in animals have only been investigated at relatively high exposure levels.

With respect to CNS effects, recent data from Echeverria and colleagues demonstrate exposure-dependent reductions in neuro-motor function and cognition without an evident threshold. However, the failure to include non-occupational control subjects in many of these studies limits their use directly as key studies for REL development.

In consideration of the above-noted factors, a modifying factor of 3 might be considered appropriate for establishing a REL for $Hg^0$ exposure in the general, non-occupationally exposed population. However, the limitations in the toxicological and pharmacological database are believed to have been adequately addressed with the application of a UF of 10 for inter-individual variability, and LOAEL to NOAEL extrapolation. Therefore, no additional MF was considered necessary.

The final adjustment for uncertainty factors is, therefore, 100.

## 7 CONCLUSIONS

Based on a LOAEL for continuous exposure of 6 $\mu g/m^3$, as determined from the study of Ngim et al. (1992), and a total adjustment of 100 for uncertainty factors, the recommended REL for $Hg^0$ in Canada is 0.06 $\mu g/m^3$. Based on currently available data and information, persons continuously exposed to $Hg^0$ at 0.06 $\mu g/m^3$ should be free of appreciable neurological, immunological or renal effects.

It is apparent from Sections 2 and 3, above, that levels of $Hg^0$ measured in the ambient atmosphere routinely fall below this REL. It is also apparent from Sections 2 and 3, above, that levels of $Hg^0$ measured in indoor air may exceed the REL from time to time, particularly where a source of metallic Hg contamination exists. As a result, research on the levels of $Hg^0$ in Canadian indoor environments (residential, commercial, institutional, etc.) would be worthwhile.

Continuous exposure to an airborne $Hg^0$ concentration of 0.06 $\mu g/m^3$ would equate to a dose in a toddler of 0.56 $\mu g$/day (inhalation rate of 9.4 $m^3$/day (HC, 2004)); continuous exposure in an adult (inhalation rate of 16 $m^3$/day (HC, 2004)) would equate to a dose of 0.96 $\mu g$/day. A daily dose exceeding this quantity could result from the presence of no more than three amalgam fillings in toddlers and five amalgam fillings in adults (0.2 $\mu g$/filling/day; after Richardson and Allan, 1996). However, it must be noted that a REL is defined in a manner to identify a level of exposure that is free of anticipated health effects. As a result, the health consequences of exceeding the Hg dose associated with this REL, as a result of possessing amalgam fillings or from other sources of exposure, cannot be determined simply by an exceedence of the REL-associated dose.

Limitations in the toxicological database were observed. *In utero* foetal exposure is evident and detrimental effects have been noted in animal studies. However, no adequate human data exist, and effects observed in animals have only been investigated at relatively high exposure levels. With respect to CNS effects, the recent data from Echeverria and colleagues demonstrate

exposure-dependent reductions in neuromotor function and cognition without an evident threshold. Given these limitations, the REL presented herein should be considered provisional in nature and re-evaluated once the dose-response relationship with respect to $Hg^0$ and subclinical neurobehavioural effects can be more precisely quantified, particularly after the methods of Echeverria et al. The NAG-Hg dose-response relationship should also be further studied and evaluated, with respect to non-occupationally exposed exposure and control groups, and controlling for confounding factors, to more precisely quantify the threshold for renal effects.

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# TABLES

Table 1.Physical-Chemical Properties of Hg0 (from CCME, 1999)

| Property | Value |
|---|---|
| Empirical formula | Hg0 |
| Molecular Weight | 200.59 |
| CAS registry number | 7439-97-6 |
| Common synonyms | hydragyrum, liquid silver, quicksilver |
| Physical state (20$^{o}$C) | heavy, mobile, liquid metal |
| Melting point (oC) | -38.83 |
| Boiling point (oC, 1 Atm) | 356.72 |
| Density (g/cm3 @ 25oC) | 13.5 |
| Electrical resistivity (μohm·m @ 20oC) | 95.76 |
| Solubility in water (mg/L @ 30oC) | 0.002 |
| Solubility in benzene (mg/L) | 2.387 |

Table 2. Estimated natural source $Hg^0$ emissions in Canada (from Richardson et al., 2003; particulate Hg omitted)

| | $Hg^0$ Emissions ($10^6$ kg/yr) | | | |
|---|---|---|---|---|
| Source | Mean | 5th Percentile [1] | 50th Percentile | 95th Percentile [1] |
| Forest & brush fires | 0.00023 | 0.000069 | 0.0002 | 0.00049 |
| Evasion from soil | 0.48 | 0.028 | 0.22 | 1.7 |
| Evasion from fresh surface water | 0.0089 | 0.0028 | 0.0085 | 0.016 |
| evasion from marine surface water | 0.027 | 0.0052 | 0.026 | 0.051 |
| Evasion from terrestrial vegetation | 0.55 | 0.41 | 0.56 | 0.66 |
| Total[2] annual $Hg^0$ emissions | 1.1 | 0.54 | 0.82 | 2.3 |

[1] The 5th and 95th percentile values provide statistically sound estimates of the lower and upper 90th % confidence limits of the mean value.
[2] Values for each statistic may not precisely sum to Total due to rounding.

Table 3. Summary of Atmospheric Releases of Mercury for the Year 2000 (EC, 2002a)

| Industry Sector | Source | Quantity Emitted (kg [1]) |
|---|---|---|
| Industrial | Primary Base Metal | 1 969 |
| | Primary Iron & Steel (includes Iron Sintering) | 88 |
| | Secondary Iron & Steel | 150 |
| | Secondary Non-Ferrous | 6 |
| | Ferrous Foundries/Ferro-Alloys | 44 |
| | Chlor-Alkali | 68 |
| | Glass Industry | 103 |
| | Cement | 313 |
| | Ashphalt | 57 |
| | Petroleum Refining | 12 |
| | Electrical Products Industry | 373 |
| | Pulp & Paper | 136 |
| | Lime Manufacture | 132 |
| | Industrial Fuel Combustion | 241 |
| | Industrial Fuel Wood | 33 |
| | Chemicals | 15 |
| | Other Industries [2] | 56 |
| | SECTOR TOTAL | 3 797 |
| Non-Industrial fuel combustion | Electrical Utilities & Non-Utility | 2 033 |
| | Residential Wood Combustion | 21 |
| | Commercial Fuel Combustion | 112 |
| | Residential Fuel Combustion | 243 |
| | SECTOR TOTAL | 2 410 |
| Transportation | Motor Vehicles | 0 |
| | Marine | 14 |
| | SECTOR TOTAL | 14 |
| Incineration | Municipal Solid Waste | 305 |
| | Sewage Sludge Incineration | 195 |
| | Hazarous Waste Incineration | 617 |
| | Industrial Incineration | 12 |
| | Biomedical | 372 |
| | Crematoriums | 140 |
| | Wood Waste Incineration | 22 |
| | SECTOR TOTAL | 1 664 |
| Miscellaneous | Fluorescent Tube Breakage | 70 |
| | Dental Amalgams | 28 |
| | Pharmaceutical Use | 0 |
| | Fungicides | 0 |
| | Sewage Sludge Application to Land | 36 |
| | Landfill Gas | 9 |
| | SECTOR TOTAL | 141 |
| | TOTAL FOR CANADA | 8 026 |

[1] Values will not add due to rounding and aggregation to protect confidentiality.
[2] Includes emissions from Gold Roasting, Carbon Black, Oil Sands

Table 4.Annual Trends in Canadian Atmospheric Emissions of Mercury [EC, 2002b)

| Year | Mercury Emissions (kg) |
|---|---|
| 1990 | 35 172 |
| 1991 | 34 595 |
| 1992 | 34 044 |
| 1993 | 18 381 |
| 1994 | 12 968 |
| 1995 | 12 150 |
| 1996 | 13 075 |
| 1997 | 10 416 |
| 1998 | 10 094 |
| 1999 | 8 531 |
| 2000 | 8 032 |

Table 5. Summary of Dental Amalgam-Related Mercury Discharges in Canada (from OAEI, 2000)

| Source | Waste Commodity | Waste Management End Product | Environmental Repository | | | |
|---|---|---|---|---|---|---|
| | | | Surface Water | Landfill | Agricultural Land | Air [1] |
| Dental Clinics | Non-Hazardous Solid Waste | Raw solid waste | | 802 | | |
| | Biomedical Waste | Incinerator ash | | 39 | | |
| | | Incinerator stack emissions | | | | 352 |
| | Wastewater | Untreated effluent | 103 | | | |
| | | STP effluent | 58 | | | |
| | | Sewage sludge | | | | |
| | | - incinerator stack emissions | | | | 157 |
| | | - landfilled ash | | 18 | | |
| | | - directly landfilled | | 175 | | |
| | | - land-spread | | | 154 | 21 |
| Human Excrement | Wastewater | Untreated effluent | 17 | | | |
| | | STP effluent | 10 | | | |
| | | Sewage sludge | | | | |
| | | - incinerator stack emissions | | | | 25 |
| | | - landfilled ash | | 3 | | |
| | | - directly landfilled | | 28 | | |
| | | - land-spread | | | 26 | 3 |
| | | REPOSITORY TOTALS | 188 | 1065 | 180 | 558 |

[1] air emissions as $Hg^0$

Table 6. Estimated $Hg^0$ exposures in the Canadian general population

| Source | Variables to derive dose | Infants (0-0.5 yrs) | Toddlers (0.6-4 yrs) | Children (5-11 yrs) | Teens (12-19 yrs) | Adults (≥20yrs) |
|---|---|---|---|---|---|---|
| dental amalgam | No of amalgam- filled teeth | 0 | 1 [1,3] | 2 [1,3] | 3 [1,3] | 6 [2,3] |
| | Dose rate [4] ug/day/amalgam-filled tooth | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| | **DOSE (µg/d)** | 0 | 0.2 | 0.4 | 0.6 | 1.2 |
| Outdoor air | [$Air_{outdoor}$] [5] (µg/$m^3$) | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 |
| | Time outdoors [6] | 1.5 hr/d | 1.5 hr/d | 1.5 hr/d | 1.5 hr/d | 1.5 hr/d |
| | Inhalation rate [6] ($m^3$/hr) | 0.09 | 0.39 | 0.6 | 0.66 | 0.66 |
| | **DOSE (µg/d)** | 0.0003 | 0.0012 | 0.0018 | 0.002 | 0.002 |
| Indoor air | [$Air_{indoor}$] [7] (µg/$m^3$) | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| | Time outdoors [6] | 22.5 hr/d | 22.5 hr/d | 22.5 hr/d | 22.5 hr/d | 22.5 hr/d |
| | Inhalation rate [6] ($m^3$/hr) | 0.09 | 0.39 | 0.6 | 0.66 | 0.66 |
| | **DOSE (µg/d)** | 0.1 | 0.44 | 0.68 | 0.74 | 0.74 |
| TOTAL ESTIMATED DOSE **(µg/d)** | | 0.1003 | 0.6412 | 1.0818 | 1.342 | 1.942 |
| TOTAL ESTIMATED DOSE (**(µg/kg-d)** [8] | | 0.012 | 0.039 | 0.033 | 0.022 | 0.027 |

[1] assumed to be 50% of 1972 values for toddlers, children, teens
- age groups most likely to have new fillings;
- 1972 values reported by Richardson and Allan (1996) and Richardson (1995);
- 40% of fillings placed in 1999 were amalgam compared to 80% in the 1980s (discussed by OAEI, 2000).

[2] assumed to be 77% of 1972 values for adults
- age group likely to have older (long term) amalgam fillings;
- 1972 values reported by Richardson and Allan (1996) and Richardson (1995);
- 23% decline is amalgam use reported between 1994 and 1999; discussed by OAEI (2000).

[3] values rounded to nearest whole number

[4] from Richardson and Allan (1996) and Richardson (1995)

[5] [$Air_{outdoor}$] = outdoor air Hg0 concentration; based on data discussed in Section 2.3.1.

[6] from HC (2004)

[7] [$Air_{indoor}$] = indoor air Hg0 concentration; based on data discussed in Section 2.3.2.

[8] Age group-specific body weights from HC (2004): infant = 8.2 kg; toddler = 16.5 kg; child = 32.9 kg; teen = 59.7 kg; adult = 70.7 kg

Table 7. Summary of Recent (post-1992) Toxicological Studies of $Hg^0$ Exposure

| Authors | Year | Findings |
|---|---|---|
| Aydin et al. | 2003 | HgU inversely related to logical memory I ($r=-0.237$, $p<0.05$) and logical memory II ($r=-0.221$, $p<0.05$) (WMS-R tests) and with total retention ($r=-0.210$, $p<0.05$) (a VTMP test). HgU were positively associated with anxiety ($r=0.217$, $p<0.05$) and psychoticism ($r=0.220$, $p<0.05$) (SCL-90-R). |
| Bittner et al. | 1998 | Significant relationship between increasing log UHg with decreasing IHST performance. Significant relationship between finger tapping general factor with age, gender, and drink frequency. Correlation between One-Hole test results and finger tapping scores, and One-Hole test results and tremor summary scores. |
| Boogard et al. | 1996 | β2M and NAG were significantly increased in the high-exposure group over the low-exposure group, however, the individual results of the workers in both groups were within the 95% confidence interval of workers who are not exposed occupationally. |
| Cardenas et al. | 1993 | Exposed group had significant reduction in the excretion of β2M, GAG, PGE2, PGF2 and TXB2 and in urinary pH. Significant increase in mean urinary NAG activity and a decrease in urinary kallikrein activity were observed in the workers exposed to the highest levels of Hg. |
| Chang et al. | 1995 | Mean N1-P1 interpeak amplitude was significantly larger in mercury group than in the controls. Significant delay of wave V latency leading to a prolongation of I-V interpeak latencies in the high-exposure group compared to controls. Significant prolonged scalp SEP latency and CCT in the high-exposure group compared to controls. |
| Discalzi et al. | 1993 | BAEPs I-V interpeak latencies were significantly different between exposed group and controls. |
| Echeverria et al. | 1995 | Significant relationship between HgU levels and poor mental concentration, emotional lability, somatosensory irritation, mood scores, vocabulary. |
| Echeverria et al. | 1998 | Significant associations between HgU and mood scales, and UHg and neurological symptoms. |
| Echeverria et al. | 2005 | Significant associations between HgU and neuro-motor functions. Statistical analysis of the association between hand steadiness and UHg could define no threshold (other than zero exposure) |
| Echeverria et al. | 2006 | Significant associations between UHg and neurolobehavioural responses in dentitists and dental assistants. UHg and a genetic polymorphism for coproporphyrinogen oxidase were additive in their association with neurobehavioral responses. |
| Ellingsen et al. | 2000 | U-NAG was statistically significantly higher in the exposed group than the reference group. U-NAG concentration was positively associated with HgU and Cum HgU/year in the regression analysis. |
| Ellingsen et al. | 1994 | Significant higher thyroglobin levels was observed in exposed subjects relative to controls. No significant differences observed between the exposed and control groups were observed for immunological endpoints (autoantibodies, immunoglobulins, complement proteins). No anti-double strand DNA, anti-nucleolar, or anti-centromere antibodies were detected in exposed workers. |
| Ellingsen et al. | 2001 | No significant differences between exposed and control subjects were observed for neuropsychological test performance. Slightly reduced performance in neuropsychological tests for visuomotor/psychomotor speed and attention, and immediate visual memory was observed in association with exposure. |
| Frumkin et al. | 2000 | Exposed subjects reported a higher prevalence of symptoms, and symptoms of greater severity, than the control group. Significant differences between the exposed and control group included: increased peroneal nerve conduction velocity, increased tremor, increased vibrotactile thresholds in fingers and toes, fewer finger taps, slower performance in the pegboard task, and poorer performance in the Hopkins Verbal Learning Test. |
| Gonzalez-Ramirez et al. | 1995 | Statistically-significant, dose-dependent detriments in a variety of neurobehavioral tests, in 10 dental technicians 5 dentists relative to 13 controls. |
| Haut et al. | 1999 | Exposed subjects had significantly reduced performance in all cognitive tests relative to controls, with the exception of the |

| Authors | Year | Findings |
|---|---|---|
| | | attention and nonverbal learning/memory tests. Exposed subjects also had significantly reduced performance in visusoperception, language score, abstraction and problem solving. In the MMPI scales, exposed subjects demonstrated significantly higher scores than controls. |
| Heyer et al., | 2004 | Significant associations between increasing UHg and increases in various self-reported symptoms and measures of mood. UHg and a genetic polymorphism for brain-derived neurotrophic factor (BDNF) were additive in their association with symptoms and mood. |
| Mathiesen et al. | 1999 | Significantly reduced performance in the visual retention test and dexterity in exposed subjects relative to controls. Significant differences in visual retention, dexterity and retention error were observed in the 25 subjects determined to have high cumulative exposures (compared to controls). |
| Moszcynski et al. | 1995 | Significantly increased counts of T-cells (CD3+), T-helper (CD4+) and T-suppressor) (CD8+) were observed in exposed workers. Lesser increases were observed in workers exposed for less than 10-years relative to workers exposed for greater than 10-years. A positive correlation was found between helper-T cell (CD4+) and exposure duration. |
| Netterstrom et al. | 1996 | Coordination performance was significantly reduced between the high-exposure group and controls. |
| Park et al. | 2000 | Significant decreases in total CD4+ and CD4+45RA+ T-lymphocytes were observed in exposed workers relative to controls. The number of CD57+CD16+ NK cells was observed to be inversely related to HgU levels. |
| Perlingeiro et al. | 1995 | Significant impairment of chemotaxis and nitroblue tetrazolium dye reduction were observed in blood samples of exposed workers relative to controls. The level of neutrophil impairment did not return to normal after 6-months of reduced exposure |
| Queiroz et al. | 1994 | Significantly increased levels of IgG, IgA and IgM were observed in exposed workers relative to controls. |
| Sandborgh et al. | 1996 | No significant changes in urinary excretion of albumin, β2-microglobulin, or NAG were observed, and the relative clearance of β2-microglobulin was unchanged. No significant correlation between HgB (blood and plasma) or HgU and renal endpoints were observed. |
| Stromberg et al. | 1999 | Significantly increased mean intensity of uro-genital symptoms was observed when intensity scores examined on an individual basis. |
| Urban et al. | 2003 | Statistically significant differences in color discrimination between the exposure and control group. |
| Warfvinge et al. | 1995 | Hg vapour exposure induced autoimmune syndrome (consistent with previous observations) in genetically susceptible mice, characterised by general stimulation of the immune system with hyperimmunoglobulinemia. |

Table 8: Summary of Key Studies Evaluated for Consideration as Basis for $Hg^0$ REL

| Effect category | Occupational group | Mean Exposure duration (Yr) | Mean UHg (μg/L) [1] | Mean Air-Hg - measured (μg $Hg/m^3$) | Air-Hg - calculated [2] (μg $Hg/m^3$) | NOAEL/ LOAEL | Observed effects | Reference |
|---|---|---|---|---|---|---|---|---|
| Neurological | Dentists, dental technicians | 5.5 | | 14 | -- | LOAEL | Decreased neurobehavioral performance | Ngim et al., 1992 |
| | Chloralkali, glass blowing, fluorescent lamp manufacture | 15.3 | | 26 | -- | LOAEL | Increased hand tremour | Fawer et al., 1983 |
| | Chloralkali | 13.7 | Exposed: 16.9 Control: 2.0 | | 26.3 | NOAEL | No significant neurobehavioural impairment | Piikivi & Hanninen, 1989 |
| | Gas production | High grp: 5.7 Low grp: 10 | High: 23.7 Low: 4.1 Control: 2.4 | | High:33.3 Low: 2.3 | NOAEL | No significant neurobehavioural impairment | Boogaard et al., 1996 |
| Renal | Gas production | High grp: 5.7 Low grp: 10 | High: 23.7 Low: 4.1 Control: 2.4 | | High:33.3 Low: 2.3 | LOAEL | Significant increase in β2M and NAG | Boogaard et al., 1996 |
| | Chloralkali | 11 | Exposed: 31.9 Control: 2.3 | | 56.1 | LOAEL | Significantly increased GAG and PGE2 | Cardenas et al., 1993 |
| | Chloralkali | 13.3 | Exposed: 10.5 Control: 2.3 | | 10.2 | LOAEL | Increased UNAG levels, suggestive of damage to renal proximal tubules | Ellingsen et al., 2000 |
| Immunological | Chloralkali | >1 to 31 yr | | Median: 36 | | LOEL [3] | Stimulation of T-lymphocites | Moszczynski et al., 1995 |
| | Fluorescent lamp manufacture | 2.6 | | 4.1 | | LOEL [3] | Reduced counts of T-lymphocytes | Park et al., 2000 |
| | Hg production/reclamation | 0.7 | Exposed: 24 Control: NR | | ND [4] | LOAEL | Impaired neutrophil function | Perlingeiro & Queiroz, 1995 |
| | Hg production/reclamation | 0.7 | Exposed: 24 Control: NR | | ND [4] | LOAEL | Increased IgG, IgA adn IgM immunoglogulin levels | Queiroz et al., 1994 |

Footnotes to Table 8:

[1] Converted to μg Hg/L as necessary; data varyingly reported as μg/L; μg/g creatinine; nmol Hg/mmol creatinine; nmol Hg/L; Hg concentration in urine is relatively constant throughout the day (Cianciola *et al.*, 1997), so urine samples collected variably as morning void, 24 hour composite, or spot sample, are comparable with respect to UHg concentration; the average creatinine content in urine is 1 g/L (Boeniger et al., 1993) and , as a result, UHg concentrations reported as μg/L and μg/g creatinine are essentially equivalent.

[2] equivalent Air-Hg concentrations derived according to Tsuji et al. (2003): log (UHg) = log(b) + 0.653 x (log(Air-Hg), where: UHg=urinary Hg concentation (μg Hg/L or μg Hg/g creatinine); b=regression Y intercept = UHg concentration reported for control subjects in the individual study; Air-Hg = airborne $Hg^0$ concentration ($\mu g/m^3$)

[3] Observed effect not confirmed as *adverse.*

[4] Not determined; no UHg concentration reported for control group and, therefore, method of Tsuji et al. (2003) could not be employed.