Supplementary materials for "Gaseous mercury limit values: definitions, derivation, and the issues related to their application"

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Summary S1 - threshold limit values for Hg

All the Hg TLVs found in literature are reported in ascending order and divided based on the duration exposure

(i.e., chronic or TWA).

- Chronic Hg TLVs

- CalEPA chronic REL for Hg^0 = 0.03 µg/m³ ([43]CalEPA 2014).

  As reported in the CalEPA factsheet, this value is derived from several occupational studies carried out

  mainly on workers employed at chloro-alkali plants ([47]Fawer et al. 1983; [48]Piikivi et al. 1984;

  [49]Piikivi and Tolonen 1989; [50]Piikivi 1989; [51]Ngim et al. 1992). All the studies point to a LOAEL of

  about 25 µg/m³ that is adjusted to a continuous exposure duration (LOAEL-ADJ) approximated to 9 µg/m³

  following the Equation (1) by US EPA ([52]IRIS 1995):

$$LOAEL\ (ADJ) = LOAEL * \frac{MVho}{MVh} * \frac{5\ days}{7\ days}$$

  Equation (1): US EPA equation used to convert an occupational LOAEL to a continuous (i.e. chronic) exposure
  duration (LOAEL-ADJ); MVh= minute ventilatory volume of air for humans (20 m³/day); MVho= minute
  ventilatory volume of air for humans in an occupational environment (10 m³/day).

  This value is then divided by a cumulative uncertainty factor (UF) of 300 which consider the use of a

  LOAEL instead of a NOAEL (UF= 10) and the interindividual variability among people (UF= 30)

  ([43]CalEPA 2014?).

- ATSDR chronic MRL for Hg^0 = 0.3 µg/m³ ([31]ATSDR 2022).

This TLV is determined starting from the clinical effects (mainly hand tremors, but also deficit in intellectual abilities) reported in several occupational exposure studies ([53]Bast-Pettersen et al. 2005; [54]Boogaard et al. 1996; [55]Chapman et al. 1990; [56]Ellingsen et al. 2001; [47]Fawer et al. 1983; [57]Langworth et al. 1992; Wastensson et al. [58]2006, [59]2008). The Hg concentrations found in worker's biomarker (i.e., urine) are converted to an equivalent Hg^0 air concentration by applying a steady-state mass balance model, i.e. an equation used to convert biomarkers Hg levels to equivalent exposure concentrations of elemental Hg vapor in air ([31]ATSDR 2022). The Hg^0 air concentration derived from the biomarkers of workers that showed neurological alterations is of 2.84 µg/m³ (95% lower confidence limit of the weighted median concentrations of the selected occupational studies): this concentration is then divided by an UF of 10 that accounts for human variability among people ([31]ATSDR 2022), resulting in the chronic MRL of about 0.3 µg/m³.

- EPA RfC for Hg^0 = 0.3 µg/m³ ([41]US EPA 2003)

  The protocol reported by the Integrated Risk Information System ([52]US EPA IRIS 1995) is substantially the same of that reported by CalEPA to derive the RELs ([43]CalEPA 2014), with the same studies cited and the same LOAEL-ADJ as starting point. The difference regards the cumulative UF used to divide the LOAEL-ADJ, that here it is of 30 (UF= 10 for protecting sensitive populations together with the use of a LOAEL and a UF= 3 due to the lack of database) instead of 300.

- WHO – Average annual Hg concentration for Hg vapour = 1 µg/m³ ([60]WHO 2000)

  WHO in the 2nd edition of its *Air Quality Guidelines* ([60]WHO 2000) proposes an average annual concentration of 1 µg/m³ for Hg vapour (chemical form not specified) as a limit for continuative (i.e., chronic) exposure. This value is calculated starting from a LOAEL spanning from 15 to 30 µg/m³, derived from an occupational study ([61]Cardenas et al. 1993) and from a WHO report ([62]WHO 1991) referring mainly to working exposures; 15 µg/m³ is considered an air Hg concentration which results in possible

renal tubular effects, while 30 μg/m³ of objective tremors ([60]WHO 2000). The LOAEL is then divided by

a cumulative UF of 20 (UF= 10 for uncertainty due to the variable sensitives in populations; UF= 2 for

using a LOAEL instead of a NOAEL). The explanation of the resulting concentration of 1 μg/m³ is instead

not reported, but probably could be assumed as a rounding of the calculation from the mean value of 15

and 30 μg/m³ divided by the UF (20).

- ATSDR action levels for indoor residential settings ([42]ATSDR 2012) = 1 μg/m³ (normal occupancy); 10

  μg/m³ (residents' evacuation/relocation)

  The action level of 1 μg/m³ for residential settings is defined "*an indoor air concentration of mercury vapor*

  that should prompt public health and environmental officials to consider implementing response actions"

  ([42]ATSDR 2012). This limit is derived based on an occupational study by Ngim et al. ([51]1992) carried

  out on a group of dentists daily exposed to elemental Hg vapour. The authors found that a Hg^0

  concentration greater than 10 μg/m³ could be considered associated with human health effects

  ([42]ATSDR 2012). This concentration is reduced by an order of magnitude (1 μg/m³) as an acceptable

  level for normal occupancy for most sensitive persons ([42]ATSDR 2012), while 10 μg/m³ is assumed as

  the action level at which the residents' evacuation/relocation is necessary ([42]ATSDR 2012).

- TWA Hg TLVs

- CalEPA 8h-REL for Hg^0 = 0.06 μg/m³ ([43]CalEPA 2014)

  Starting from the occupational studies reported for the CalEPA chronic REL ([98]Piikivi and Hanninen

  1989; [47]Fawer et al. 1983; [49]Piikivi and Tolonen 1989; [50]Piikivi 1989; [51]Ngim et al. 1992), the LOAEL

  of 25 μg/m³, adjusted (following the Equation 1) to 18 μg/m³ (i.e., twice than the LOAEL-ADJ used for the

  chronic exposure), assuming that the ventilation rate for humans during a working-day is half (10 m³/day)

that of the whole day (20 m³/day). The LOAEL-ADJ-8h (18 μg/m³) is then divided by the same cumulative UF used for the chronic REL (UF= 300).

- CalEPA acute REL for Hg^0 = 0.6 μg/m³ ([43]CalEPA 2014)

  CalEPA releases also an acute REL for Hg^0 referring to a one-hour intermittent exposure. Based on the absence of acute inhalation studies on humans, the starting point to derive this REL is the study of Danielsson et al. [63] (1993) carried out on a group of pregnant rats exposed to 1.8 mg/m³ (assumed as the LOAEL) of Hg^0 vapor for 1h- or 3h-day during gestation. The LOAEL is then divided by a cumulative UF of 3000 (UF= 10 for the use of a LOAEL instead of a NOAEL; UF= 30 for the interindividual variability among people; UF= 10 for the toxicodynamic differences between rats and humans, these last potentially with a greater developmental susceptibility) ([43]CalEPA 2014).

- ATSDR action levels for workplaces not covered by the 29 CFR 1910 Subpart-Z = 3-4 μg/m³ ([42]ATSDR 2012)

  The 29 CFR 1910 Subpart-Z is the document of the 29th Title of the Code of Federal Regulation dealing with occupational safety and health standards on workplaces. The Subpart-Z of this Title is a list of TLVs that must be applied in that workplaces where an exposure to a toxic compound is expected. Regarding Hg, the Subpart-Z must be applied in occupational settings, mainly industrial, where a Hg exposition for workers has to be expected. In the occupational settings where a Hg exposure is not an expected hazard, such as customers or clients in businesses or students in a school, ATSDR proposes a TLV in the range of 3-4 μg/m³ ([42]ATSDR 2012). These values are derived starting from the residential action level (1 μg/m³), which is calculated on a 168-hour exposure (24h/day) or a 112-hour exposure (16h/day) adjusted to an occupational exposure (40h/week) typical of a commercial or public workplace (168 is four times longer than 40 and 112 is three times longer) ([42]ATSDR 2012).

- European Union 8-hour TWA IOELV = 20 μg/m^3 ([46]Directive 2009/161/EU, regulatory limit)

  The topic of occupational Hg pollution is dealt with by the European Union (EU) in the Directive 2009/161/EU that establish an occupational Hg 8h-TWA of 20 μg/m^3. The Directive, transposed by all the EU member states, reports a list of several TLVs for chemical compounds, which are indicative occupational exposure limits (IOELVs). The IOELV values are established by the European Commission, assisted by the Scientific Committee for Occupational Exposure Limits to Chemical Agents (SCOEL). SCOEL deals with the occupational exposure limits to Hg in its SCOEL/SUM/84 (last update, May 2007[33]): the suggested TLV for Hg^0 (20 μg/m^3) is derived by the Hg levels in biomarkers, i.e. 35 μg/g creatinine for urine, and 9 μg/L in the blood, associated with and indicative central nervous system toxicity effect ([65]Roels et al. 1985; [64]Williamson et al. 1982; [48]Piikvi et al. 1984). The conversion between Hg concentrations in biomarkers to Hg level in the air is derived using the ratios 1:0.7 (mg/m^3:mg/l) for urine and 1:0.48 (mg/m^3:mg/l) for the blood (see references in [33]SCOEL/SUM/84), that result in the Hg airborne levels of 25 μg/m^3 and 20 μg/m^3, respectively. The lowest value among the two (20 μg/m^3) is chosen as the health-based occupational exposure level for Hg^0. The SCOEL summary adds that a skin notation for this Hg form is not appropriated based on the potential contribution to systemic body burden ([33]SCOEL 2007).

- ATSDR action levels for workplaces covered by the 29 CFR 1910 Subpart-Z = 25 μg/m^3 ([42]ATSDR 2012)

  The derivation method is not present; the authors refer to the ACGIH 8h-TWA reported in the book "*Threshold limit values for chemical substances and physical agents & biological exposure indices*" ([66]ACGIH 2009).

- ACGIH – TLV (8-hour TWA) for inorganic Hg forms including metallic Hg = 25 μg/m^3 ([66]ACGIH 2009)

  A clear explanation of the 8h-TWA derivation method is not present ([66]ACGIH 2009), although the presence of the BEI (Biological Exposure Index) for Hg^0 in urine (20 μg/g creatinine) suggest that the air

concentration of 25 μg/m^3 Hg could be derived by this value. However, a urine-air conversion factor is not reported ([66]ACGIH 2009).

- Cal/OSHA – PEL (8-hour TWA) for metallic Hg and inorganic compounds = 25 μg/m^3 ([69]OSHA 1989, regulatory limit)

  The derivation method of the 8h-TWA is not present.

- WHO – Recommended occupational exposure (TWA) = 25 μg/m^3 ([67]WHO 1980)

  WHO reports several occupational studies to derive the recommended occupational exposure to Hg^0, a TWA with no time limitations specified. Based on all the data of the cited researches, WHO concluded that non-specific symptoms arise at an exposure of about 50 μg/m^3 to Hg^0, while workers may be expected to have tremors after a long-term exposure to 100 μg/m^3. With a health-based approach, WHO affirms that a careful TLV of 25 μg/m^3 would ensure a reasonable degree of protection ([67]WHO 1980).

- NIOSH REL (10h-TWA) = 50 μg/m^3 ([73]NIOSH 1973).

  The derivation method of the 10h-TWA is not present, while a skin notation is specified ([73]NIOSH 1973).

- OSHA 8-hours TWA = 50 μg/m^3 and ceiling value = 100 μg/m^3 of the ([69]OSHA 1989, regulatory limit)

  These concentrations refer to Hg^0 and are derived from several occupational studies ([70]Rentos and Seligman 1968; [71]Smith et al. 1970; [72]Danziger and Possick 1973): all the authors find that adverse effects to vapour Hg exposure occur at concentration ranging between 50 and 100 μg/m^3, thus assumed by OSHA as an 8-hours TWA and a ceiling limit, respectively. The same ceiling value is reported by NIOSH as a ceiling REL, i.e. a "*value that should not be exceeded at any time*" ([73]NIOSH 1973).

- WHO – Recommended occupational short-term exposure = 500 µg/m^3 ([67]WHO 1980).

The recommended occupational short-term exposure released by WHO at 500 µg/m^3 is based on the evidence that a short-term exposure in the range of 200-1000 µg/m^3 give rise to pulmonary effects on workers: as reported above, a precautional and health-based approach provides the value of 500 µg/m^3 as TWA (time limitations not reported) that must not be exceeded ([67]WHO 1980).

- NIOSH IDLH (immediately dangerous to life or health) TLV = 10,000 µg/m^3 ([74]NIOSH 1994).

This value refers to all inorganic Hg compounds: as reported by NIOSH [74] (1994), IDLHs were based on the effects that might occur as a consequence of a 30-minute exposure. This value is the highest TLV for Hg found in the current scientific literature.

- EPA AEGLs (acute exposure guideline levels, [41]EPA 2010).

EPA AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels C AEGL-1, AEGL-2 and AEGL-3 C are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects.

The three AEGLs are defined as follows: AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it

is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

AEGLs ($\mu g/m^3$) for gaseous Hg are reported in the table below:

	exposure duration				
	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	N.D.	N.D.	N.D.	N.D.	N.D.
AEGL 2	3100	2100	1700	670	330
AEGL 3	16000	11000	8900	2200	2200

AEGLs-1 values for Hg^0 are not recommended due to insufficient data.

AEGL-2 is derived by a single 2-hour exposure of pregnant rats to 400 $\mu g/m^3$ mercury vapor (Morgan et al. 2002). The exposure to 400 $\mu g/m^3$ was a NOAEL for developmental effects in rats. The 400 $\mu g/m^3$ value is divided by a total uncertainty factor of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3) based on a weight of evidence approach and the incompatibility of the derived values with monitoring data if a larger uncertainty factor is used.

AEGL-3 values is derived by the 1-hour exposure of rats to 26700 $\mu g/m^3$ (Livardjani et al. 1991). A 2-hour exposure at this concentration resulted in significant mortality. The 26700 $\mu g/m^3$ value is adjusted by a total uncertainty factor of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3) based on faster uptake in rodents compared with humans and the incompatibility with monitoring and accidental exposure data if a larger uncertainty factor is used. The uncertainty factor of 3 is considered sufficient to protect susceptible populations.