Occupational Health Clinics for Ontario Workers Inc.
Centres de santé des travailleurs (ses) de l'Ontario Inc.

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May 31, 2022

American Conference of Governmental Industrial Hygienists (ACGIH)
1330 Kemper Meadow Drive
Cincinnati, Ohio 45240
Attention: Threshold Limit Values for Chemical Substances Committee

Re: Submission to the ACGIH TLV® Committee

The Occupational Health Clinics for Ontario Workers Inc. (OHCOW) is a not-for-profit labour governed worker-based network with a team of dedicated health professionals committed to promoting the highest degree of physical, mental and social well-being for workers and their communities. We strive to accomplish this through the identification of workplace factors which are detrimental to the health and well-being of workers; by empowering workplace parties to make positive occupational health changes in their workplaces. Our clients include workers, joint health and safety committees or representatives, unions, employers, health professionals, community groups, legal clinics, students, and members of the public.

At seven clinics in Ontario, Canada, an interdisciplinary team of client service coordinators, occupational health nurses, occupational hygienists, ergonomists, and contract physicians offer clinical and prevention services for both individual patient and larger cluster investigations providing an objective, evidence-based opinion on whether an illness or injury may be work-related. promote awareness of health safety issues, evaluate occupational exposures, and develop prevention strategies. OHCOW's unique experience, and vulnerable worker lens, provide a unique perspective on a full circle occupational illness/disease prevention approach (primary, secondary and tertiary) and as such, continue to provide leadership to Ontario's Occupational Illness Prevention System Focus.

Please find attached our separate submissions following your guidelines for: Aluminum, Diesel Exhaust, Lead, Nickel and nickel compounds not including nickel carbonyl, Welding Fumes, and three anesthetic gases- Desflurane, Enflurane and Sevoflurane.

Thank you for the opportunity on behalf of our team.

Sincerely,

Kimberly O'Connell

Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP
Executive Director, OHCOW
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Date Submitted: May 31, 2022

Chemical Substance **Aluminum**
(5 pages + citable materials)

Name of Group/Individual Submitting Comments: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
Authored by: Kevin Hedges, Ph.D., M.App.Sc, COH, CIH, Occupational Hygienist
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Executive Summary *(limit 250 words)*

Recent findings from literature for McIntyre Powder-related publications have demonstrated that inhaled aluminum can translate into the bones, as detected by neutron activation analysis. The method provided by Bicklet et al. 2022 demonstrated that in vivo neutron activation analysis could measure bone aluminum levels in 15 miners who had been exposed to McIntyre Powder over 40 years prior.

Demers et al. 2020 noted that when looking at the rate of Parkinson's disease and Parkinsonism, there was a 27% and 14% increase in incidence rates of both, when compared to the general population.

This information reaffirms that there may be a risk from neurodegenerative disease, which provides the impetus for the ACGIH® to establish a BEI® for aluminum.

Specific action: proposing a BEI® for aluminum in urine of 50 µg/g creatinine based on the work of Klotz and Hartwig (2020).

Chemical Substance: Aluminum
Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**
Specific Action Requested
1. It is recommended the ACGIH® consider proposing a BEI® for aluminum in urine of 50 µg/g creatinine based on the work of Klotz and Hartwig (2020).

Rationale

The ACGIH® feasibility assessment (2007) notes:

> "The Committee has concluded that since there is not currently a pattern of neurobehavioral testing results unambiguously related either to air exposure at the TLV or to urinary aluminum excretion levels, it is not feasible at this time to establish a urinary Aluminum BEI based on neurobehavioral health effects".

There are pertinent papers that can be used to guide the establishment of a biological exposure index that are complementary to Laureys and Hoet 2001. In addition, the reference list in the feasibility assessment is well short of that provided in Lauwerys and Hoet 2001, third edition.

In addition, a series of papers related to former miners' exposure to McIntyre Powder, exposure, characterization, and levels of Al detected in the lungs from autopsies of former miners and Al in bone detected in retired miners some 40 years after exposure and health effects including neurodegenerative disease provides useful study source material. McIntyre Powder is an aluminum and aluminum hydrooxide powder that was historically used in some mining sectors (mandatorily prescribed by the employer) as an "inhaled prophylaxis" hypothesized to prevent silicosis prior to each shift in varying doeses. It was later found not to have this intended effect and in fact has been shown to have caused other adverse health effects (neurodegenerative disease and contributed to other respiratory diseases).

From the study by Verma 2019, the grand mean level of aluminum was found to be 476.4 µg/g of dry lung tissue, which is similar in the range reported for occupationally exposed groups. As there were elevated levels of aluminum in bone reported by Bickley et al. 2022, this indicates that translocation did occur into the bones which may also indicate a likelihood for translating of aluminum particles into brain tissue.

Regarding air monitoring, aluminum in bone and health effects, a recent paper by Bickley et al. 2022, and the papers related to the use of McIntyre Powder has quantified and characterized exposure to McIntyre Powder (Zarnke et al. 2019) and evaluated Aluminum in bone some 40 years after exposure for 15 retired miners (Bickley et al. 2020). The inverse variance weighted mean was still significantly higher than the control group inverse variance weighted mean (17.30 ± 2.30 vs. 3.51 ± 0.85 µgAl/gCa, $p < 0.001$). Results from this study compared to the Mohseni (cited in Bickley et al. 2022), both the control subjects and the cases. The inverse variance weighted mean of the Alzheimer's Disease subjects was 12.35 ± 0.97 µgAl/gCa, with high levels of 37.4 ± 5.35 µgAl/gCa and 31.6 ± 6.11 µgAl/gCa. There is overlap between the Alzheimer's Disease subjects and these retired miners, but the miners had higher bone Aluminum levels, based on the inverse variance weighted means (Bickley et al. 2022).

A recent cohort study by Demers et al. 2020, investigated the association of McIntyre exposure with

neurodegenerative diseases. Data were pulled from the Mining Master File (MMF), an electronic database recording medical records and work history from 90,000 miners across Ontario. During the period of McIntyre powder use, 28% of all underground miners were exposed, with the peak being 24.5% of all miners in 1961.

Of these exposed miners, 90% were exposed after 1956. When looking at the rate of Parkinson's disease and parkinsonism, there was a 27% and 14% increase in incidence rates of both compared to the general population. When compared with miners that had never been exposed to McIntyre Powder, there was a 34% and 19% increase in incidence of both. This pilot study was able to demonstrate that aluminum can be measured in the bones of miners exposed to McIntyre Powder over 40 years ago. This technique could potentially be applied in further cross-sectional studies of health effects in this group (or similar groups) of workers. The increased bone aluminum was detectable in about half the subjects measured even 40 years after the exposure to McIntyre Powder had ceased. With adjustments for biological removal of aluminum from bone over time, the maximum concentration detected is in line with values reported from a previous study measuring aluminum levels in dialysis patients, suggesting similar initial exposure levels.

Recently, a meta-analysis of eight epidemiological studies found that chronic aluminum exposure was significantly associated with increased risk of AD (OR = 1.71, 95% CI: 1.35–2.18) (Wang et al. 2016). Krewski et al. (2007) also indicated that approximately 60% of the body burden is in the bone. Aluminum in bone has a long half-life (likely several years) and is slowly released to the blood (Poddalgoda et al. 2021).

The results from this study combined with results of a study by Zarnke et al. (2019), where miners inhaled aluminum nanoparticles mostly in the form of **aluminum hydroxide** are useful when trying to understand both the bioavailability and body burden of McIntyre Powder.

The biological half-life for aluminum in bone has been estimated to be between 10 and 20 years (Priest 2004). Further analysis of this data set, including extrapolating and estimating past urinary aluminum levels based on back calculated correlations between exposure to McIntyre Powder may reveal the urinary aluminum levels at this time. Table 2.2 of Laureys and Hoet 2001, including a study by Mussi et al. 1984, which shows a correlation coefficient – r, of 0.9267 for electric welding, polishing and shape cutting. The derived formula is Al-U µg/L = -15.7 + 36.4 Al – A mg/m^3.

Further evaluation of Lauwerys and Hoet (2001, table 2.2, p.27) is warranted, which should also guide to establishing a BEI® for aluminium.

The German Federal Environmental Agency (Umweltbundesamt) established provisional reference values for the general population using concentrations of aluminium in both urine and serum, which amount to <15 µg/L and <5 µg/L, respectively (Klotz et al., 2017). However, it should be noted that these provisional reference values are not health-based guidance values and do not take into consideration the toxicity of the substance; they only represent current background exposure in the general population, and therefore are based upon exposure data only.

Poddagolda et al. 2021, reported the for oral exposure to aluminium, including a Minimal Risk Level (MRL) by the Agency for Toxic Substances and Disease Registry (ATSDR), a Provincial Tolerable Weekly Intake (PTWI)

by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and a Tolerable Weekly Intake (TWI) by the European Food Safety Authority (EFSA).

In the derivation of their chronic minimal risk level (MRL), the ATSDR (2008) considered several animal studies examining the chronic toxicity of aluminium. Ultimately, a lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day was chosen for neurological effects in mice exposed to aluminium lactate in the diet during gestation, lactation and postnatally until 2 years of age (Golub et al., 2000). ATSDR (2008) derived a chronic MRL of 1 mg/kg bw/day by applying an uncertainty factor (UF) of 300 (3 – extrapolation from a LOAEL to a no observed adverse effects level (NOAEL), 10 - interspecies variation, 10 - intraspecies variation) and a modifying factor of 0.3 to account for the greater bioavailability of aluminium lactate compared to other aluminium compounds to which the general population are exposed.

An MRL of 137 µg/L has been provided for aluminum in urine. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure (ASTDR 2017).

The German DFG in their evaluation of a biological reference value (BAR), which represents the background exposure of persons of working age occupationally not exposed to aluminium, have established a level of 15 µg/g creatinine (Sampling time: for long-term exposures: at the end of the shift after several shifts). A biological reference value (BAR) representing the background exposure of persons of working age occupationally not exposed to aluminium is presented; this value is oriented towards the 95th percentile (DFG 2019). This value is 50 µg aluminium/g creatinine (µg/l: 1.2 µg Al/l = 1 µg Al/g creatinine).

In 2017, a BAT value for aluminium of 50 µg/g creatinine was established, which is based on effects described in the addendum of 2018 (translated 2019, Klotz et al. 2019). As critical end point neurotoxicity was considered (DFG 2019).

BAT values (“Biologische Arbeitsstoff-Toleranz-Werte”: biological tolerance values) and BLW (“Biologische Leit-Werte”) to enable the evaluation of the risk to an individual’s health which results from exposure to a substance at the workplace. BAT values can be established only for substances which can be taken up by the body in substantial quantities via the lungs and/or other body surfaces (skin, gastrointestinal tract) during occupational exposure. Another prerequisite for the establishment of a BAT value is that sufficient occupational-medical and toxicological data are available for the substance and that these data are supported by observations in man.

The German DFG (2021) BAT value for aluminum in urine is 50 µg/g creatinine equivalent to 60 µg/L considers the **critical point for neurotoxicity**. Therefore, we recommend that the ACGIH® considers the literature from the McIntyre Powder project, and information provided by Klotz and Hartwig (2020) when considering a BEI® for aluminum.

Conclusions

This submission recommends consideration proposing a BEI® for Al in urine of 50 µg/g creatinine based on the work of Klotz and Hartwig (2020).

Citable Material

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Date Submitted: May 31, 2022

Chemical Substance **Diesel Exhaust**
(10 pages + citable materials)
Name of Group/Individual Submitting Comments: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
Authored by: Kevin Hedges, Ph.D. M.App.Sc, COH, CIH, Occupational Hygienist.
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Executive Summary *(limit 250 words)*

Elemental Carbon (EC) is used as an indicator of diesel exhaust by most jurisdictions. The European Union has recently decided on an occupational exposure limit of 0.05 mg/m^3 EC, in effect from 2023. Germany and Sweden also have a limit of 0.05 mg/m^3 EC. Other jurisdictions have 0.1 mg/m^3 (GESTIS nd.). The Australian Institute of Occupational Hygiene recommends a limit of 0.1 mg/m^3 EC measured in the "submicron fraction" to avoid contamination from larger interfering respirable carbon particles. Cherrie 2019 noted that a limit of 0.1 mg/ m^3 EC "would do little to reduce the predicted death toll from occupational exposure to diesel exhaust particulate". In 2001, the ACGIH® proposed a TLV®-TWA of 0.02 mg/m^3 based on EC as determined by NIOSH Method 5040; however, this was withdrawn a year later.

Short term health effects haven't typically been considered when considering an OEL of 0.05 mg/m^3 EC (BAuA 2017). Based on the findings of Anderson et al (2019), reported health effects from a short-term exposure to 0.0103 mg/ m^3 over just 3 days of exposure from diesel exhaust generated in passenger trains.

This submission recommends a TLV®-TWA of 10 µg EC/m^3 with (L) notation as an evidence-based limit for all workplaces. In addition, OHCOW recommends a TLV®-TWA of 60 pg/m^3 for 1-nitropyrene (1-NP). The current literature indicates that 1-aminopyrene (1-AP) concentration in urine would provide an excellent biomarker of exposure which would complement personal exposure monitoring for 1-NP, and warrants consideration in future.

Chemical Substance: Diesel Exhaust

Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document**

Specific Action Requested

1. This submission recommends a TLV®-TWA for diesel exhaust measured as elemental carbon (EC) at 10 µg/m^3 or 0.01 mg/m^3 with the (L) notation, an abbreviation of "exposure to all routes should be carefully controlled to level as low as possible." This can be measured following NIOSH Method 5040 (sub-micron EC) with improvements to sampling and analysis provided in Noll et al 2020 to improve sensitivity / detection. This will ensure that the Limit of Quantitation (LOQ) is no more than 10% of the proposed TLV®-TWA.
2. This submission recommends a second complimentary TLV®-TWA for diesel exhaust based on exposure to 1-nitropyrene; using the correlation between EC and 1-NP. Riley et al (2018) noted that 1-NP is predicted an increase of ~6 pg/m^3 for 1-NP per 1 µg/m^3 increase in EC which equates to 60 pg/m^3.
3. This submission recommends a BEI® for 1-aminopyrene (1-AP). The literature indicates 1-AP concentration in urine would provide an excellent biomarker of exposure which would complement personal exposure monitoring for 1-NP.

Rationale

Introduction

Due to new diesel engine technologies, there has been a significant reduction in emissions in recent years. There are orders of magnitude differences in emissions from diesel engines (Khalek et al 2011) – older versus new. Chronic inhalation studies on rats with diesel exhaust from **"new diesel engine technology"** (Mauderly 2010; HEI, 2015b) result low exposure ranges (highest concentration about 10 µg/m^3 diesel soot particles provided no evidence of pulmonary carcinogenicity. For older technology engines, a recent expanded reanalysis of previous pooled case-control analysis on diesel exhaust and lung cancer by Ge et al 2020, has reaffirmed findings from previous meta-analysis. In this study, Excess Lifetime Risks (ELR) associated with 45 years of EC exposure at 50, 20, and 1 µg/m3 were 3.0%, 0.99%, and 0.04%. Included in the study were 16,901 lung cancer cases and 20,965 control subjects (Ge et al 2020). These pooled studies reported that exposure to diesel exhaust measured as EC at 1, 10, and 25 mg /m^3 would result in 17, 200, and 689 extra lung cancer deaths per 10 000, respectively, by the age of 80 years (Taxell and Santonen 2017).

Even at very low exposure levels there is a consistent exposure–response relationship between EC and lung cancer in men. They note that reduction of workplace EC levels to background environmental levels will further reduce lung cancer ELR in exposed workers. According to the German Committee for Hazardous Substances - AGS Management - BAuA - www.baua.de/ags (2017): **"the critical effect is particle-related chronic inflammation in the lungs".** If this chronic inflammation is avoided, it is assumed that there is no additional cancer risk from diesel soot. A threshold effect (chronic particle-related inflammation) is considered the most probable for lung tumor development and an AGW for diesel soot, as EC, is derived. The PAHs and nitro PAHs "attached to the soot core are associated with

genotoxicity". For the endpoint of chronic particle-related inflammatory effect, Mauderly et al (1987) derived an OEL of 50 μg EC/m³ for rats. As the soot coreis believed to be the cause of the chronic effect of diesel engine emissions; therefore, the derivation is based on the EC. **This assessment however is based on "chronic effects" rather than "acute effects".**

AGS 2017 derived particle-related inflammatory effects are based on chronic exposure. Acute exposures are not used to derive the limit value. This is important and in fact the TLV®-TWA should consider short term (acute) health effects as chronic health effects will be compounded from acute health effects. Regarding simultaneous exposure to other substances such as nitrogen oxides, separate air limit values must be observed. According to AGS (2017, for Benzo(A)Pyrene (BaP), and other polycyclic aromatic hydrocarbons (PAH), the PAH adsorbed on the diesel soot and acceptable risk for BaP overall cannot be assigned any relevant significance, with regard to the carcinogenic effect at an OELof 50 μg EC/m^3. The estimated additional risk from PAH and nitro-PAH adsorbed on the soot core is noted below the acceptable risk of 4:100,000 (AGS 2017). From chronic inhalation studies in rats, derived after extrapolation to lower risk levels for exposure to specified as EC in μg/m³ determined an acceptance risk of 4:100,000 from a Human Equivalent Concentration (HEC) of 24 μg/m^3 (AGS 2017). However, a recent study by Anderson et al (2019) demonstrated health effects for 29 healthy volunteers over a period of 3 days exposed to diesel exhaust while sitting as passengers in diesel-powered trains.

The effects noted in the study by Anderson et al (2009) included reduced lung function, altered heart rate variability, and increased levels of DNA strand breaks; as compared with those exposed to electric trains. The exposure average for black carbon (BC) (approximately the same as EC) was 10.3 μg/ m^3 over 3 days of exposure. Other indicators of exposure may be important as discussed further in this submission.

1-NP as a surrogate / replacement for EC, which may also provide a better exposure marker, and which may be complimentary (tracked) from biological monitoring for 1-AP in urine.

Setting a suitable TLV® considering analytical and technical feasibility measuring Elemental Carbon (EC)

Considering analytical limitations for EC, the limit of quantitation (LOQ) is 20 μg/m^3 or 0.02 mg/m^3. The level that can reliably be measured, is commonly referred to as the LOQ, minimum reported value (MRV), or limit of reporting (LoR). According to Birch (2016) with a 960-L air (full shift) sample, an LOD translates to an air concentration of about 2 μg/m^3, which is the LOQ. Considering the accuracy of NIOSH 5040 for EC, which is ± 16.7% at 23 μg/m^3, and that the LOQ is ~ 2 μg/m^3 NIOSH (2016), this will limit measurement at lower concentrations. NIOSH notes that a working range of approximately 6 to 630 μg/m^3, with an LOQ of ~ 2 μg/m^3 for a 960-L air sample. This requirement is described in ISO 15202- 35, and BS EN 482:20126 requires that the measuring range of the procedure or instrument shall cover the concentration from 0.1 times to 2 times the OEL. As noted, an accuracy of NIOSH 5040 of **± 16.7% at 23 μg/m^3**, with an LOQ of ~ 2 μg/m3 NIOSH (2016), limits the TLV®-TWA to no less than 20 μg/m^3, the same level proposed by the ACGIH in 2001. This requirement is also reinforced by Verpaele, S (2018). EN 482 also states that every procedure should operate within the range of 0.1–2 times the occupational exposure limit values (OELVs). In the European context, the LOQ should be no more than 0.1 or 10% of the limit.

Will assigning a TLV®-TWA of 0.1 mg/m^3 in line with many jurisdictions greatly reduce the health impact?

A limit of 0.1 mg/m^3 respirable elemental carbon (REC) provided by many jurisdictions may not have a profound health impact. A health-based limit would be around 0.00001 mg/m^3, resulting in an estimated four extra deaths from lung cancer per 100 000 exposed for 40 years, as has been proposed by the Dutch Health Council (DECOS). This limit is clearly impracticable because it is below the levels typically found in ambient air in most city streets. Due to analytical feasibility at least for NIOSH 5040, an LOQ restricts the TLV®-TWA to no less than 20 µg/m^3. More recently, Noll et al 2020, reported that when compared with the standard cassette, the new high-sensitivity cassette designed by NIOSH improves the limit of detection of NIOSH 5040 by approximately five-times (Noll et al 2020).

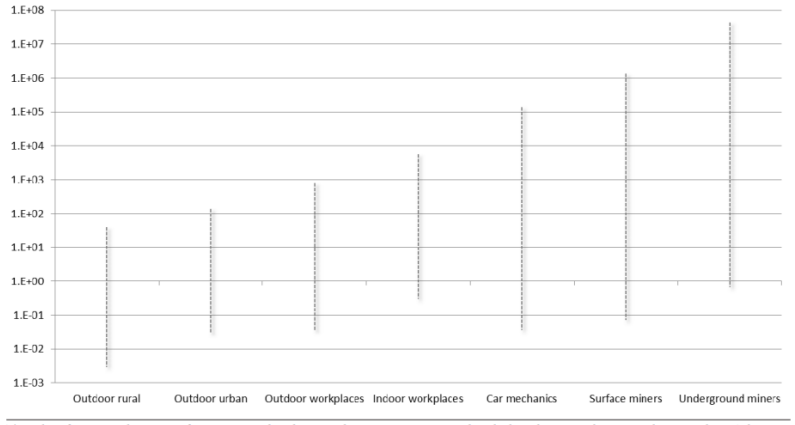
Measurement of personal exposure to nitropyrene when exposures are below 20 µg/m^3 EC

A major constituent of diesel exhaust is nitropyrene. 1-nitropyrene (1-NP) is the most abundant nitroarene in diesel emissions, and its formation is facilitated by the high temperature and excess air supply in the combustion chamber of diesel exhaust, where it is generated by the addition of nitrogen oxide or nitrogen dioxide to free pyrene radicals (IARC 2018).

A recent study to evaluate of 1-NP as a surrogate measure for diesel exhaust found high correlations between the quantiles of 1-NP and EC exposures. This means that 1-NP may in fact be a better surrogate, especially when assessing personal exposure < 20µg/m^3 EC. One potential advantage of 1-NP compared to EC as a surrogate measure of diesel exhaust, is the absence of confounding sources of 1-NP in a typical mine environment.

Nitropyrene is probably carcinogenic to humans (Group 2A) (IARC 2018). A robust linear relationship for each quantile of the task groups for EC and 1-NP is shown by Riley et al 2018 where 1-NP is predicted to increase ~6 pg /m^3 for a 1 µg m^3 increase in EC. Therefore, taking the Finnish and Occupational Cancer Research Centre (OCRC) recommended limit of 5 µg/m^3 (EC) this equates to ~ 30 pg/m^3 1-NP; or applying ~6 pg/m^3 per 1 µg/m^3 increase in EC, 10 µg/m3 would equate to ~ 60 pg/m^3 1-NP.

In addition, to further understand what an appropriate limit for 1-NP would be, although outdated (1992 to 1998), figure 1.1 in IARC 2018 (monograph 105) can be used for comparison.



The values for car mechanics, surface miners and underground miners were measured in the breathing zone by personal air sampling. Other values were the results of air sampling at fixed locations (stationary high-volume sampling). The results presented in this figure are also summarized in Tables 1.4–1.7.
Compiled by the Working Group.

Range of air concentrations of 1-nitropyrene in ng/m3 (Source IARC monograph 105 1-ntropyrene 2018 p. 643.

Can a lower diesel exhaust (elemental carbon (EC)) TLV®-TWA be achieved?

Mining

Underground miners are considered the most highly exposed IARC 105. In Australia, Peters et al (2016) determined from 8,614 personal EC measurements from 146 different jobs at 124 mine sites between 2003 and 2015, expressed as arithmetic mean exposures, were: 0.018-0.026 mg/m^3 for surface occupations (equivalent to geometric means of 0.008-0.011 mg/m^3); and 0.03 – 0.10 mg/m^3 for underground occupation groups (equivalent to geometric means of 0.017-0.059 mg/m^3). For 2011, job specific EC geometric mean exposures were: 0.01-0.019 mg/m^3 for surface operators over a 12-hour shift and 0.014-0.059 mg/m^3 for underground operators. Jobs with the highest geometric mean exposure levels underground were diesel loader operators, ground, or roof support occupations (including shot-creters) and non-contract miners (including miners operating a jumbo or handheld drilling rig), with EC exposure levels of 0.059, 0.055 and 0.053 mg/m^3 for a 12-hour work shift at a gold mine in 2011, respectively AIOH (2017).

In Ontario Canada, a survey representative of 12 mines demonstrated personal exposure results with a geometric mean (GM) (n = 118) of 0.03 mg/m^3 for underground miner personal samples taken in 2018. Year by year analysis demonstrated a reduction of about 0.0024 mg/m^3 per year, which should translate to about 0.0156 mg/m^3 in 2024 as a result of continuous improvement. An international goal set by BHP Billiton (Multi-national mining company) to reduce diesel exposures to "as low as technically achievable" has achieved personal exposures to within 0.03 mg/m^3 (EC) for both international coal and metal mines (McDonald R, 2016 MSHA submission). This reaffirms that setting a lower TLV®-TWA is a key driver to reducing exposures (Hedges, 2017). This company - in its mines in Canada - has also reported substituting electric engines for diesel wherever possible to eliminate all diesel exhaust exposure, and further reduce diesel exhaust exposure.

Workplaces other than mining

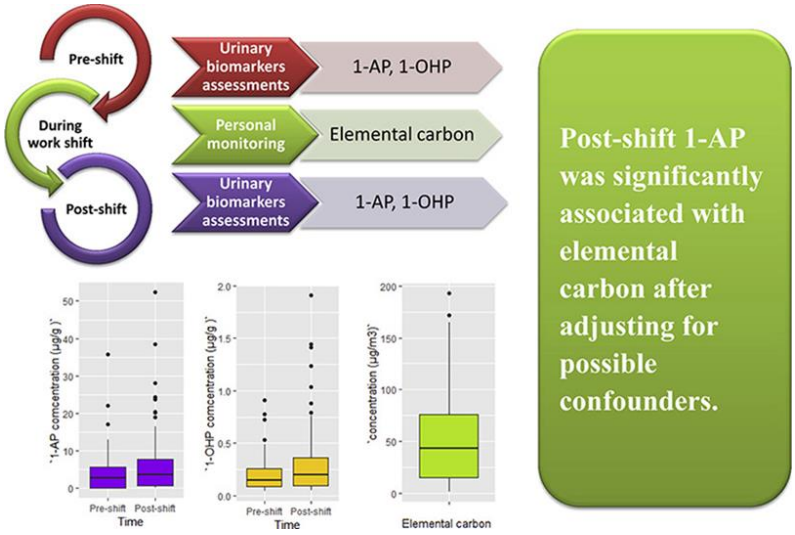
Plato et al (2020) provides "A historical job-exposure matrix for occupational exposure to diesel exhaust using EC as an indicator of exposure". This Finnish job-exposure matrix (FINJEM) used specific exposure to diesel and gasoline exhaust over different time intervals (3–15 years) between 1945 and 2003. Results from this JEM representative the year 2000 demonstrate many exposures to EC within 10 µg/m^3 (Plato et al 2020). Couch et al (2016), evaluated EC concentrations in US fire stations in 2016 and reports all results for 3 fire stations < 0.01mg/m^3. However, it is likely that with statistical analysis the upper confidence limit (UCL) (95% Lands Exact) will exceed 0.01 mg/m^3.

A study by Anderson et al (2019) demonstrated health effects for 29 healthy volunteers were exposed to diesel exhaust while sitting as passengers in diesel-powered trains. Exposure to diesel exhaust inside diesel-powered trains for JUST 3 days was associated with reduced lung function and systemic effects in terms of altered heart rate variability and increased levels of DNA strand breaks compared with electric trains as previously discussed. The exposure average for black carbon (BC) (approximately the same as EC) was 10.3 µg/ m^3 the average for the electric train was 1.8 µg/m^3. In a study by Jeong et al (2017), side by side monitoring was carried out in different sections of a diesel-powered passenger train. At the front of the train directly behind the diesel-powered engine the average concentration was shown to be 22 µg/m^3 (BC equivalent to EC). This is a location where the train balance crew are located. The same monitoring for a train in "push mode" and not "pull mode" resulted in a marked reduction of BC to well within 10 µg/m^3; meaning that if a TLV®-TWA were assigned as 10 µg/m^3 an impetus for continuous improvement would drive reduction.

Biological monitoring

In addition to the value of direct measurement of 1-NP exposure in air as a surrogate measure of diesel exhaust exposure, air measurements of 1-NP could be useful to validate biomarkers of exposure to diesel exhaust, including measurements of 1-NP metabolites in urine or measurements of hemoglobin adducts to 1-aminopyrene. Moreover, as many of the nitro-arenes, including 1-NP, are mutagenic and carcinogenic (IARC, 2014), measurements of 1-NP and its metabolites may better reflect the carcinogenic properties of diesel exhaust (Riley et al 2018, Ramsay 2015). A practical, sensitive method for measuring 1-aminopyrene in human urine using a HPLC-fluorescence technique has been developed (Laumbach et al 2009). 1-aminopyrene was found by Gong et al 2015 to be associated more strongly with diesel combustion products. 1-Nitropyrene (1-NP) is a major nitro-polycyclic aromatic hydrocarbon (nitro-PAH), and a common constituent in diesel exhaust particles (DEPs). There is a significant correlation between 1-NP exposure and urinary 1-AP concentration; therefore, urinary 1-AP level could be used as an exposure biomarker for DEP (Ochirpurev et al 2022). In a study by Du et al (2019), and consistent with the sensitivity analysis, the concentrations of two urinary biomarkers, 1-AP and 1-hydroxypyrene (1-OHP), increased significantly across a 12-hour mining work shift in all participants. After adjusting for potential confounders and covariates, post-shift 1-AP was significantly associated with EC exposure.

For every 10% increase in the concentration of EC there was a 4.0% increase in the concentration of post-shift creatinine-corrected 1-AP.



- EC measured as a surrogate of diesel exhaust by personal monitors
- Urinary 1-AP and 1-OHP increased significantly across a 12-hour work shift.
- 1-AP showed a robust and significant association with EC

Source: Du et al 2019, Measurement of urinary 1-aminopyrene and 1-hydroxypyrene as biomarkers of exposure to diesel particulate matter in gold miners, Graphical abstract

Ultrafine particles, $PM_{2.5}$, NO_2

Short-term exposures to ambient ultrafine particles (UFPs) (<0.1 μm) have been associated with acute changes in physiological measures of cardiorespiratory health (Wellek & Blettner 2012, Evans et al 2014). More recently, Lavigne et al 2020 evaluated a total of 1,066 childhood cancers that were identified. They found that first trimester

exposure to UFPs (Hazard Ratio (HR) per a particle count, 10,000/cm^3 increase = 1.13, 95% CI: 1.03–1.22). This was associated with overall cancer incidence diagnosed before 6 years of age after adjusting for $PM_{2.5}$, NO_2, and for personal and neighborhood-level covariates. Although not an occupational exposure, this is mentioned as there is potential it poses an increased risk in occupational exposures.

Cancer

As noted, the International Agency for Research on Cancer (IARC) has concluded that diesel exhaust is a cause of lung cancer (Group 1: carcinogenic to humans). CAREX Canada estimates that approximately 897,000 Canadians are currently exposed to diesel exhaust at work. Approximately 2.4% (OCRC) to 6% (Vermeulen et al 2014) of annual lung cancer deaths may be due to diesel exhaust exposure. Combined data from three U.S. occupational cohort studies including more than 40,000 workers in the trucking and mining industries (Vermeulen et al 2014) have provided a powerful estimate of the risk of lung cancer based on the level and duration of exposure to diesel exhaust. The SHEcan project also predicted that around 230 000 people will die from lung cancer from workplace exposure to diesel exhaust particulate in the EU (Cherrie 2019). The truckers' study Garshick et al (2012) and miners' studies Silverman et al (2012), (Attfield et al 2012), (Stewart et al 2010) combined, allows for a determination of the risk of lung cancer based on the level of exposure to diesel exhaust.

A move towards a process of continuous improvement rather than just meeting a minimum standard is particularly relevant when considering a TLV®-TWA for diesel exhaust (Cherrie et al 2019).

Understanding what is technically feasible or as low as reasonably achievable is relevant. To this point, we recognize that a leading mining company prior to 2016 reduced exposure levels to as low as reasonably achievable and achieved at least as low as 0.030 mg EC/m^3 for international mining operations (McDonald R 2016). Notwithstanding, OHCOW acknowledges the OCRC Burden of Occupational Cancer in Ontario (2017) proposed OELs that align with the Finnish Institute for Occupational Health, which recommends occupational exposure limits of 20 μg/m^3 EC for the mining industry and 5 μg/m^3 EC for other workplaces. This recommendation is based on evidence of health effects and feasibility considerations.

The data of the German Potash Miners Cohort are suitable for quantitative risk assessment with respect to diesel exhaust and lung cancer, despite the smaller number of lung cancer cases in comparison to the Diesel Emissions in Mines Studies (DEMS). The underground workplaces in Potash mines examined in both studies have similar diesel exhaust exposure intensities. However, the range of cumulative exposure in the Potash study is not as wide as almost all workplaces were located underground. Information on confounding factors in the Potash study were restricted to entry into the mine, data on former mining, and crude information on smoking status. Nevertheless, the results of the reanalysis of this cohort support the notion that a clear relationship between diesel exhaust and lung cancer is absent, at least in the range of a cumulative REC exposure up to 2.5 mg/m^3-years. According to Mohner and Wendt (2017), the formerly suspected strong relationship between diesel exhaust and lung cancer based on the original analysis of the long-term follow-up of the cohort is misleading due to methodological shortcomings such as adjustment for time since hire. Mohner and Wendt (2017), noted that in view of the results from animal studies and the fact that a threshold model cannot be ruled out, a conservative lower bound for a possible threshold value should be determined. They did note that an upper bound for the cumulative exposure of 2.5 mg/m^3-years of REC seems to be sufficient to prevent a detectable increase of lung cancer risk. This value corresponds to an average annual value of 50 μg/m^3 REC assuming a working life of 45 years. In 2017, Dr. Vermeulen provided a presentation through the OCRC in which he concluded

that the "acceptable risk" and "maximum tolerable risk" levels for diesel exhaust would be below 1 µg/m^3 EC. Such limits are below current occupational exposure levels, and in some instances even below environmental exposure levels.

OHCOW acknowledges the policy recommendations in the OCRC report "Burden of Occupational Cancer in Ontario OCRC 2017, p.251) to adopt occupational exposure limits of 20 µg/m^3 EC for the mining industry and 5 µg/m^3 EC for other workplaces based on the Finnish Institute for Occupational Health. A single limit of 10 µg/m^3 across all workplaces provides a practical TLV®-TWA, although it may take industry some time to achieve this level if using older diesel engines. The technology is however available to currently achieve exposures at this level.

A TLV®-TWA of 10 µg /m^3 will also provide more of an impetus for continuous improvement and target those workplaces with greatest risk. Taxwell and Santonen (2016) note that abed on a log-linear meta-regression model, 45 years of occupational exposure to diesel exhaust at 1, 10 and 25 µg EC/m^3 was estimated to result in 17, 200 and 689 extra lung cancer deaths per 10 000 individuals, respectively, by the age of 80 years. In addition, DECOS 2019 notes 4 extra death cases of lung cancer per 1,000 (prohibition risk level), for 40 years of occupational exposure, equals to 1.03 µg REC/m^3. Thus a health based TLV®-TWA would have to be within 1 µg/m^3 EC, which is currently not feasible.

Based on the available data, the critical health effects of diesel exhaust are pulmonary inflammation and lung cancer (Taxwell and Santonen, 2017). Setting a health based TLV® for cancer is currently not feasible. The ACGIH terminology for an (L) should therefore be provided along with the TLV®, **"exposure by all routes should be carefully controlled to levels as low as possible"**. For lung inflammatory changes, from human inhalation studies (1 – 2hr), the inflammatory changes in bronchiolar lavage (BAL), bronchial wash (BW) and increased airway resistance from exposure to (older technology) diesel exhaust, diesel exhaust particles have been assessed. The lowest observable adverse effect level is 0.1 mg/m^3 (Taxwell and Santonen, 2017) mg/m^3) (DECOS 2019). In 2017, the federal Ausschuss für Gefahrstoffe (AGS) derived an occupational exposure limit for diesel exhaust of 50 µg EC/m^3 (8-h TWA).

The AGS also provided qualification that in animal experiments lung tumours were observed after exposure to particulate matter is explained by inflammation (chronic irritation). Thus, the AGS considered irritation and lung inflammation the critical effect against which workers should be protected. According to DECOS (2019), 0.1 mg/m^3 diesel exhaust particles approximates to 0.075mg/m^3 EC, although this is questionable if it will apply to all diesel engines. This is empirical, and the ratio will not be constant with a wide variation. Nasal, throat and eye irritation is described in experiments with healthy human volunteers after a single exposure to inhaled diesel exhaust (concentrations of exhaust varying from 108 to 300 µg diesel exhaust particles/m^3 (≈ 81 to 225 µg EC/m^3).

In addition, in healthy human volunteers, single exposure to diesel exhaust for two hours induced pulmonary effects (e.g., lung inflammation, lowered lung function). These effects were observed at exposure levels of the exhaust varying from 100 to 300 µg diesel exhaust particles/m3 (≈ 75 to 225 µg EC). The AGS noted that experiments with humans on single exposure to diesel exhaust were not considered useful, since the increase in inflammatory parameters were related with the NO_2 in the exhaust. The AGS also gives suggestions for risk-based limit values (e.g., acceptable (4:100,000) and tolerable risks (4:1,000)) for the carcinogenic effects. Based on the animal experiments, it suggests an "acceptable risk" concentration level of 20 µg EC/m^3 (24 µg EC /m^3 HEC equivalent) (TRGS 900, table 2). The US EPA estimates that the ambient outdoor level of diesel exhaust (<10 µm particle size measured by EC) would be up to 1-3 µg/m^3. In analysis of exposures in the trucking industry NIOSH estimated that a 13 µg/m^3 working life exposure was associated with a 1-2% (10-20/1000) excess risk of lung cancer above the 5% background lung cancer risk. The

EPA has developed a reference concentration (RfC) for diesel exhaust of 5 μg/m^3 of diesel exhaust (roughly equivalent to 3.1-6.6 μg/m^3 of diesel exhaust as determined by EC) which was derived based on dose-response data on inflammatory and histopathological changes in the lung from rat inhalation studies. There is the question of exposure to other gases (sulphur compounds, other nitrogen oxides, VOCs, etc.). The EPA (page 1–7) states: "Effects of diesel exhaust exposure could be additive to or synergistic with concurrent exposures to many other air pollutants. … (e.g., potentiation of allergic effects, potentiation of diesel exhaust toxicity by ambient ozone and oxides of nitrogen)". Recently new papers have been released particularly dealing with the lung cancer risks associated with exposure to diesel exhaust.

In 2014, Bob Park from NIOSH reviewed the risk estimates associated with a working lifetime exposure to diesel exhaust and the risks of developing lung cancer (Park 2014). The range of lifetime equivalent concentrations to diesel exhaust (measured as REC) associated with a risk of 1/1000 (maximum occupational risk benchmark) was 0.32-0.94 μg/m^3. "Approximately 1.4 million workers were exposed to DEE during the risk exposure period. The initial estimated AFs for DEE-related lung cancers are: 4.92% for males, 0.29% for females, and 2.70% overall." (Reference 10, page A37; AF = attributable fraction, DEE = diesel exhaust). Five percent of Canada's working population are exposed to diesel exhaust at work according to CAREX Canada. In Ontario, more than 300,000 workers are exposed. A recent report concluded these exposures cause 170 lung and 45 bladder cancers in workers annually. This same report also highlighted a significant regulatory gap in Ontario citing a complete lack of occupational exposure limits (OEL) for whole diesel exhaust or diesel particulate matter. Regarding public consultation on a proposed legislated OEL for diesel, the level being proposed falls well short of what scientists believe is needed to protect exposed workers. The Ontario Ministry of Labour and Skills Development proposed an OEL of 160 μg/m^3 for diesel exhaust measured as total carbon and more recently they revised this to 0.12 mg/m^3 EC; as noted above, the OCRC (based in Ontario) recommends lowering any occupational exposure limits to 20 μg/m^3 (EC) for the mining industry and 5 μg/m^3 (EC) for all other workplaces.

Total Carbon versus Elemental Carbon (EC)

In addition, relying on total carbon as a surrogate for diesel exhaust has been demonstrated to be a less sensitive and less accurate measure than EC. EC is a better measure of exposure and less prone to interferences than total carbon (TC), therefore the limit should be set as EC, not total carbon. According to Debia et al (2017): "The variability observed in the TCR/ECR ratio shows that interferences from non-diesel related organic carbon can skew the interpretation of results when relying only on Total Carbon data". Because the mechanisms of lung cancer in humans are likely to be multifactorial, including direct genotoxicity, diesel exhaust particle-induced oxidative stress and pulmonary inflammation, Taxell and Santonen 2017, believe that it is currently not possible to identify a threshold level for carcinogenicity. In addition, when the pulmonary inflammatory response seen in controlled human studies after 1–2 h exposure at 100 μg diesel exhaust particulate/m^3 (approximately 75 μg EC/m^3) the OEL should be well below this level. There is sparse data available to link high exposure to new technology diesel exhaust with pulmonary inflammatory effects, without indicating genotoxicity or carcinogenicity (Bemis et al, 2015; Hallberg et al, 2015). The Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, derives so-called health-based calculated occupational cancer risk values 4 (HBC-OCRVs) associated with excess cancer risk levels of 4 per 1,000 and 4 per 100,000 as a result of working life exposure. The Committee estimates that the concentration of EC from diesel exhaust in the air, which corresponds to an excess cancer risk level of:

- 4 deaths per 1,000 for 40 years of occupational exposure, equals to 1.03 μg EC/m^3,
- And 4 deaths per 100,000 for 40 years of occupational exposure, equals to 0.011 μg EC/ m^3.

Since the estimated HBC-OCRV of 1.03 µg EC/m^3 falls in the range of the ambient urban air levels (0.4 – 2.0 µg EC/m^3), and the HBC-OCRV of 0.011 µg EC/m^3 is even far below these levels, DECOS recommends that workers should not be exposed to diesel exhaust at levels higher than the background levels. For the Public, Health Canada (2016) in its "Human Health Risk Assessment" for Diesel Exhaust noted that based on traditional risk assessment methodologies, and with regard to general population exposures, a short-term exposure guidance value of 10 µg/m^3 and a chronic exposure guidance value of 5 µg/m^3 have been derived based on diesel exhaust to protect against adverse effects on the respiratory system.

Health Canada (2016) considers bladder cancer along with respiratory effects, cardiovascular effects, immunological, reproductive, and central nervous effects. It is likely that quantitative analysis of the population health impacts associated with the contribution of diesel exhaust to criteria air contaminant concentrations in Canada will drive reduction (Health Canada 2016).

Conclusion

Anderson et al (2019) in a presentation delivered by Hedges and Jeong (2021), demonstrated exposure to diesel exhaust inside diesel-powered trains for 3 days was associated with reduced lung function and systemic effects in terms of altered heart rate variability and increased levels of DNA strand breaks in peripheral blood mononuclear cells (PBMCs) when compared with exposures for those on electric trains. The average concentration for diesel train occupants, over 3 days, reported by Anderson et al (2019) was 10.3 µg/m^3 TWA.

Therefore, based on this study to reduce the risk from both short term and long-term health effects a TLV®-TWA of 10 µg/m^3 (EC) is recommended. This will drive the reduction from health impacts of non-cancer related on lung health as well as reduce the burden of lung and bladder cancer. In addition to the above, measurement of 1-nitropyrene is complimentary. 1-nitropyrene (1-NP) is more specific of an indicator for cancer causing effects from exposure to nitroarenes (Scheepers et al 1995) and measurement is more sensitive at lower concentrations than EC. 1-NP measurements can differentiate exposures associated with specific work tasks more effectively than EC, and 1-NP may be more sensitive to differences in diesel exhaust composition (Riley et al 2018). When considering an appropriate TLV®-TWA for 1-NP, Riley et al 2018 provides a reference from which correlations against EC can be interpolated.

Providing a TLV®-TWA for diesel exhaust, measured as Elemental Carbon (EC) of 10 µg EC mg/m^3 is feasible with current technology. OHCOW recommends this be adopted as the TLV®-TWA, along with the (L) notation. Further, OHCOW recommends a TLV®-TWA for 1-nitropyrene as a complimentary measurement for diesel exhaust, set at 60 pg/m^3.

In addition, there is a significant correlation between 1-NP exposure and urinary 1-aminopyrene (1-AP) concentration, meaning that 1-AP would provide an excellent biomarker of exposure which would complement personal exposure to 1-NP.

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Chemical Substance **Lead**
(6 pages + citable materials)

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Executive Summary *(limit 250 words)*

Exposure to lead has been associated with cardiovascular disease, reproductive, central nervous system, renal, hematological, and carcinogenic health effects. The body burden of lead exposure on workers is mainly determined by the measurement of blood lead levels (BLL). According to the Centers for Disease Control and Prevention (CDC), all exposure to lead can induce pathology, with BLL > 5 µg/dL the threshold considered to be elevated in both children and adults (CDC 2021). Workplace lead exposures below the current TLV®-TWA can result in a BLL higher than those that have been shown to cause adverse health effects. To adequately protect workers, an updated lead TLV® needs to be established. Several legislative bodies in Europe have proposed lowering the occupational exposure limits and biological exposure limits due to documented adverse health effects at levels below the current ACGIH® TLV®-TWA of 0.05 mg/m^3.

We recommend the TLV®-TWA be lowered to 0.004 mg/m^3. This exposure limit would be in line with the proposal set by European Chemical Agency (ECHA) and Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), which adopted this value based on a derivation of 0.004 mg/m^3 corresponding to 15 µg/dL for blood lead (0.7µmol/l). As noted above, the CDC recommends BLL < 5 µg/dL. Furthermore, as we also recommend the (L) notation and the (Skin) notation to ensure adequate protection for the workers. Finally, we recommend the ACGIH® BEI® be lowered to 15 µg/dL (or 150 µg/L) to correspond to this proposed TLV®-TWA.

Chemical Substance: Chemical Name

Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**

Specific Action Requested

1. It is recommended that the ACGIH® TLV®-TWA be reduced from 0.05 mg/m^3 to 0.004 mg/m^3 to ensure protection from both the carcinogenic effects, renal, hematological effects, and the most sensitive toxic effects, namely damage to the nervous system.
2. We recommend the current TLV®-TWA include the (L) notation, an abbreviation of "exposure to all routes should be carefully controlled to level as low as possible.
3. We recommend the current TLV®-TWA include the (skin) notation, based on evidence of this as a pathway for exposure.
4. We recommend the ACGIH® BEI® be lowered to 15 µg/dL (or 150 µg/L). This would correspond to the TLV®-TWA proposed in this submission.

Rationale

1. Review of Other Guidelines

The Australian Institute of Occupational Hygienist (AIOH) provided a supplementary guidance value of 0.03 mg/m^3, stating that where there is potential for lead in air to exceed 0.03 mg/m^3, or where a risk assessment indicates a need, a lead biological monitoring program is required. It further suggested for system to be implemented to prevent or significantly reduce exposure for females of reproductive capacity to ensure blood lead to be less than 5µg/dL (AIOH Exposure Standards Committee, 2018).

IARC have reported that humans occupationally exposed to lead show evidence of genotoxicity, and in some studies these effects were correlated with detectable blood lead concentrations. It did further note that all the human genotoxicity studies involved co-exposure to lead and other compounds; therefore, the evaluation of lead's attributable role to genotoxicity alone needs additional investigation (IARC, 2006).

European Chemicals Agency (ECHA) provided an opinion paper on scientific evaluation of Occupational Exposure Limit (OEL) for lead and its compounds and the committee for risk assessment (RAC) evaluation derived an 8-hour TWA of 0.004 mg lead/m^3 (inhalable fraction) for lead and its inorganic compounds. The Biological Limit Value (BLV) is derived to be 15 µg/dL lead blood for lead and its inorganic compounds. ECHA further states:

> "the application of a Biological Limit Value (BLV) is to be preferred over an air limit value since internal lead levels are decisive for the chronic toxicity of lead and its inorganic compounds. Nevertheless, an air limit value complementary to the BLV is also proposed. However, due to the potential additional exposure resulting from ingestion due to hand mouth behaviour, which could significantly affect internal exposure, the air limit value may not sufficiently protect from exceedance of the BLV" (European Chemical Agency (ECHA), 2020).

Biological reference value of 3 µg/dL lead for women and 4 µg/dL lead blood for men was established as result of the re-evaluation by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area in 2019 (Göen & Drexler, 2020). The following year, the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) presented the 57th List of Maximum Workplace Concentrations (MAK values) and Biological Tolerance Values (BAT values) in 2021. In the list, the Commission has arrived at new assessments for lead and its inorganic compounds. Based on new findings on carcinogenic effects and organ damage caused by lead, it was possible to change the previous classification from carcinogenicity category 2 (carcinogenic in animal experiments, no threshold limit value possible) to category 4 (carcinogenic, mechanism known, threshold limit value evaluable). As a result, the Commission derived a BAT value of 150µg/dL blood lead.

It is not possible to make simple conversions from occupational lead concentrations in the air to concentrations in the blood of workers. By means of complex mathematical modelling, however, it was demonstrated that a MAK could be inversely derived as 0.004 mg/m^3 from the BAT value (DFG, 2022). Due to the adverse effect of lead on the developing nervous system, however, a risk to an unborn child must be assumed even if the BAT or MAK value is complied with; therefore, lead has been assigned to pregnancy group A (DFG, 2022).

Although there are various studies that have shown BLL as low as 3.4 µg/dL is associated with adverse health effects such as genotoxicity, the DFG derived airborne concentration value should be considered and we recommend the ACGIH reduce the current TLV®-TWA to 0.004 mg/m^3 to ensure protection from both the carcinogenic effects and the most sensitive toxic effects, namely damage to the central nervous system.

2. Review of Recent Literature and Documents for Low Level Lead Exposure and Multiple Routes of Exposure

Lead is absorbed predominantly from respiratory and digestive system, though some skin absorption can occur. The effect of lead exposure in respiratory, neurological, digestive, cardiovascular, and urinary disorders, and the role of inflammatory, immune-modulation and oxidative mechanisms in inducing these disorders, are well investigated and reviewed. Lead can disturb the inflammatory system and result in increased inflammatory mediators in human, experimental animal and cell culture systems. One of the main mechanisms underlying the toxic effects of lead on respiratory, nervous, digestive, cardiovascular and urinary systems is inflammation. Therefore, there are complicated immune network and regulatory pathways underlying this inflammatory process. Lead exposure at low to moderate levels induces immune disregulatory effects. Similar to asthma, lead-induced immunotoxicity via pronounced shifting in the balance in T helper cell function towards the T helper-2 sub type cells. Lead-caused inflammatory cascade induction in the central nervous system via activating of glial cells, impairing the blood-brain barrier function and over expression of inflammatory mediators.(Boskabady et al., 2018). Clinical and epidemiological studies published in recent decades have demonstrated the adverse impact of cumulative low- to moderate level lead exposure and the development of significant adverse health effects, even with BLLs in the range of 10-20 µg/dL (0.483 µmol/L – 0.966 µmol/L) (Holland et al., 2016).

The Association between Low Level Lead Exposure and Cardiovascular Health

A population-based cohort study of low-level lead exposure and mortality in US adults showed that of the 14 289 adults studied, the geometric mean concentration of lead in blood was 2.71 µg/dL. Of the participants, 20% had a concentration of lead in blood of at least 5 µg/dL. During median follow-up of 19.3 years, 38% of the study population died from cardiovascular disease, and 22% from ischaemic heart disease. An increase in the concentration of lead in blood from 1.0 µg/dL to 6.7 µg/dL, which represented the 10^{th} to 90^{th} percentiles, was associated with all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality. This data demonstrated low-level environmental lead exposure substantially affected cardiovascular health (Lanphear et al., 2018). With respect to BLL and cardiovascular-related markers in adults, significant associations between BLL, diastolic blood pressure, and high-density lipoprotein cholesterol was found in a recent case study. For systolic blood pressure, there was a significant elevation when comparing individuals with low BLL of 0-2 µg/dL and individuals with higher BLL of 2-5 µg/dL; and even more difference were found with higher BLL of 5-10µg/dL. This indicates a potential relationship between higher lead exposure and increasing systolic blood pressure (Obeng-Gyasi et al., 2018).

A recent case study of the effects of low BLL (BLL<10µg/dL) on hypertension among male workers indicates that both diastolic and systolic blood pressure were statistically significantly associated with BLL (6.87-10.00µg/dL). Moreover, the odds ratio (OR) of hypertension increased with each 1 µg/dL increment in BLL, suggesting a dose-response relationship. In other words, lower levels of lead in blood than the current occupational safety standards were shown to elevate blood pressure (Kim et al., 2020).

A recent case study of e-waste recyclers further provides evidence that detrimental effects such as hazardous cardiovascular and hematological effects of lead are observed among chronically lead-exposed workers, despite their exposure was within permissible levels (Upadhyay et al., 2021).

A positive association between low BLL (mean= 2.20 µg/dL) and higher diastolic blood pressure was also found in the US National Health and Nutrition Examination Survey (NHANES) 1999-2016 study (Teye et al., 2020).

Significant association between BLL and hypertension was found in a case study of communication radio-repair workers in Thailand (Thongsringklee et al., 2021).

In a 2020 pilot study of allostatic load, a measure of chronic stress and cardiovascular disease. Among individuals exposed to lead found that in comparison to lower lead-exposed (<5 µg/dL) individuals, lead-exposed (>5 µg/dL) individuals exhibit higher chronic stress indicators and may experience adverse cardiovascular health outcomes. Furthermore, this study did demonstrate positive association between BLL of 3 µg/dL and increased oxidative stress and inflammatory responses (Obeng-Gyasi & Obeng-Gyasi, 2020).

The Association between Low Level Lead Exposure and Renal Dysfunction

A case study of paint workers with normal blood pressure and blood lead level as low as 4 µg/dL were found to have elevated risk of renal dysfunction (OR=2.784, 95% CI: 1.475-5.25) (X. Wang et al., 2018). A case-cohort

study investigating the impact of chronic lead exposure on liver and kidney function and haematologic parameters found there was a significant relationship between BLL and white blood cell and serum urea, hepatic transaminases and creatinine (Nakhaee et al., 2019). A recent meta-analysis further observed the association between BLL exposure and abnormal renal function test parameters. Based on the findings, this study suggests that workers who have an excessive BLL of 30 µg/dL should be removed from their job and return to work when their BLL drops below 20 µg/dL (Kuraeiad & Kotepui, 2021).

The Association between Low Level Lead Exposure and Genotoxicity

A case study of the health-related outcome of lead exposed lead-acid battery plant workers demonstrated significant dose-response relationship between lead exposure and expressions of hematological toxicity and genotoxicity. This study identified benchmark dose for lead induction of micronuclei and telomere length changes to be 6.6 µg/dL and 3.5 µg/dL respectively. (T. Wang et al., 2020) Further study of the association of BLL with multiple genotoxic biomarkers among workers in China indicated that low dose exposure to lead (median = 17.4 µg/dL (8.9-26.4 µg/dL)) can still cause health hazards to an occupational population; and the mechanism may be via the induction of DNA and chromosome damage. (T. Wang et al., 2021).

The epigenetic changes in sperm DNA attributable to lead exposure is recently investigated and the result indicates that aberrant DNA methylation of the calcium homeostasis pathway, induced by low Lead exposure (5-10 µg/dL), is the potential cause for reduced sperm velocity (Zhang et al., 2021).

The effect of low-level lead exposure to prenatal women is significant, and female workers who are exposed to lead in the work environment have been demonstrated to require more protective limits. A meta-analysis investigating the association of maternal lead exposure with the risk of preterm showed a direct and significant association of maternal BLL with risk of preterm birth. It was reported that at BLL >10 µg/dL, an increase of 1 µg/dL in BLL was correlated with gestation length decrease by 0.3 days (Habibian et al., 2021).

Multiple Routes of Exposure

A case study of brass foundry workers' estimated lead body burden from different exposure routes indicated that although lead air concentration was well below the Swedish occupational exposure limit value (exposure <0.1-3.4 $\mu g/m^3$), the BLL was in the range of <0.72-33 µg/dL. Further, lead on skin surfaces, after performing normal work tasks during a 2 hours period, was in the range of 0.2-48 $\mu g/cm^2$. Based on their analysis, the authors conclude that hand-to-mouth behaviour resulting in ingestion yielded the highest contribution (16 µg/dL BLL), followed by skin absorption (3.3-6.3 µg/dL BLL) and inhalation (2µg/dL BLL). Therefore, skin absorption of inorganic lead and its contribution to systemic dose needs to be considered. (Julander et al., 2020).

Animal Study

In animal studies of adult mice, it was found exposure to the lowest (30 ppm lead acetate, mean BLL 3.4 µg/dL) and highest (330 ppm lead acetate, mean BLL 14.1 µg/dL) levels of lead during early development had similar disruptive effects in the neuroimmune system and had long-term consequences on different synaptic properties of

at least two hippocampal synapses. As such the consequences of early lead exposure might worsen the cognitive decline observed in aging men and women. (Tena et al., 2019; Dominguez et al., 2019)

Conclusion

There is emerging evidence that individuals chronically exposed to lead can exhibit detrimental effects such as hazardous cardiovascular, renal, and hematological effects at levels lower than the TLV®.

To ensure adequate protection of workers given the complexity of the exposure routes, OHCOW recommends the (L) notation, an abbreviation of "exposure to all routes should be carefully controlled to level as low as possible" to be added to the current TLV®-TWA value. To reflect the recent evidence of skin absorption as a route of exposure, OHCOW recommends the (Skin) notation.

Furthermore, the Occupational Exposure Limit set out by the European Chemicals Agency (ECHA) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) of 0.004 mg/m^3 for lead and its inorganic corresponding to a BLL of 15 µg/dL is an evidence-based approach. Thus, we recommend that the ACGIH® reduce the current TLV®-TWA of 0.5 mg/m^3 to 0.004 mg/m^3. We recommend the ACGIH® BEI® be lowered to 15 µg/dL (or 150 µg/L) to correspond to this submission's proposed TLV®-TWA.

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Date Submitted: May 31, 2022

Chemical Substance **Nickel and nickel compounds not including nickel carbonyl**
(10 pages + citable materials)

Name of Group/Individual Submitting Comments: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
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Executive Summary

The carcinogenicity of nickel compounds and nickel metal is confirmed (IARC, 2012). Many industries will have a mix between insoluble and sparingly soluble nickel species which is why one limit should apply. With additional supporting information around health effects including cancer, reproductive toxicity, and pneumoconiosis / fibrosis, OHCOW recommends a significant reduction to the TLV®-TWA from 0.1 to 0.01mg/m^3 for inhalable nickel. A 0.01mg/m^3 TLV®-TWA should apply to both soluble and sparingly soluble nickel.

Thirteen cohorts of nickel workers (~100,000 workers) demonstrated no excess cancer risk was observed in these studies when exposures to nickel in the inhalable aerosol fraction were kept ≤0.1 mg Ni/m^3 (Oller et al. 2014). SCOEL (2011) also report inflammatory responses/fibrosis in the lung which is the basis for their OEL of 0.005 mg/m^3 for respirable nickel. ECHA have set a limit for nickel and its compounds of 0.005 mg/m^3 in respirable dust. The setting an OEL at this level may be limited due to the limit of quantitation not being low enough (Verpaele 2019).

Assigning one limit as 0.01 mg/m^3 for inhalable nickel and compounds (both sparingly soluble and soluble) should be protective for fibrosis and be more practical. Due to reproductive toxicity of nickel compounds, a BEI® is recommended as this will go hand in hand with personal exposure monitoring. A BEI® of 10 µg/ L is recommended.

Chemical Substance: <u>Nickel and nickel compounds not including nickel carbonyl</u>
Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**
Specific Action Requested
1. Consider assigning one TLV®-TWA for nickel and its compounds measured as inhalable nickel as 0.01 mg/m^3 for "both" soluble and sparingly soluble nickel and mixed nickel species. 2. Due to the carcinogenicity of nickel and mixed nickel species and reproductive toxicity include the note from the endnotes / abbreviations an (L) "exposure to all routes should be carefully controlled to levels as low as possible." 3. Due to the sensitizing health effects include in the notations DSEN (dermal sensitization) and RSEN (respiratory sensitization). 4. Biological monitoring of exposure is complimentary to personal exposure monitoring. Therefore, both the traffic light approach outlined in this document should be considered along with considering assigning a BEI® for nickel in urine at 10 µg/L.

Rationale

Reproductive health effects / developmental toxicity

The European Union has classified some forms of nickel as reproductive category 2 (based on animal studies), H360D, which is attributed to chemicals that may damage the unborn child (AIOH, 2016).

The Office of Environmental Health Hazard Assessment 2018, provide information on analyses of pregnancy complications included 290 Ni refinery workers and 336 non-Ni workers. They show pregnancy complications in Ni refinery compared with other workers, and malformations among the specific Ni refinery occupations and non-Ni workers. Reproductive health effects are reported, and correlations are made with nickel in urine concentrations. In a study of more than 300 Russian nickel-refinery workers compared with local construction workers, normal pregnancies were reduced in the nickel workers compared with the non-nickel worker from an average of 39% to 29%, whereas spontaneous abortions were increased from 9% to 16%, and structural malformations in live births increased from 6 to 17% (Chashschin, et al., 1994). Nieboer (2006) concludes that animal studies suggest that "water-soluble nickel salts cause developmental toxicity to rodents in the absence of general or maternal toxicity in adult animals. If one adds to this the clear evidence in humans that nickel is transferred across it seems prudent to classify water-soluble nickel compounds as if they cause developmental toxicity. Previous studies of nickel exposure have demonstrated increased an increased risk to the fetus including spontaneous abortion and birth defects (Chashschin et al. 1994), and for an exposure to a breast feeding infant from nickel in breast milk (Frazier et al. 1998).

Due to the risk of exposure for women of reproductive age since nickel freely passes the placental barrier; knowing how much nickel is present and whether women of reproductive age have a likelihood of being exposed must be considered an important component of a biological monitoring program.

It should also be noted that in Europe there are requirements for managing pregnant and breastfeeding workers.

Cancer (Mixed soluble, sparingly soluble, and insoluble nickel and carcinogenicity).

There is debate about whether soluble nickel compounds are carcinogenic. Oller (2002) cited in AIOH 2016, concluded that the weight of evidence indicated that inhalation exposure to soluble nickel alone will not cause cancer. However, Oller conceded that if soluble nickel is inhaled at concentrations high enough to induce chronic lung inflammation, these compounds may enhance carcinogenic risks associated with inhalation exposure to other substances. Further evidence clearly indicates that these compounds strongly increase the potency of oxidic nickel compounds and should be considered as carcinogenic (Goodman et al. 2009, cited in AIOH 2016). Under the European Union Classification, Labeling and Packaging (CLP) legislation, many soluble and insoluble nickel compounds are classified as Carc 1A, stating that these compounds are known to have carcinogenic potential for humans, based largely on human evidence. This classification specifies inhalation as the only route of concern. Nickel metal is classified as Carc 2, suspected human carcinogen based on evidence from animal studies. Likewise, IARC classified soluble and insoluble nickel compounds under Group 1, carcinogenic to humans, and nickel metal and alloys under Group 2B, possibly carcinogenic to humans.

Analyses of dose-responses for the main chemical forms of nickel (soluble, oxidic and sulfidic compounds) that included 13 cohorts of nickel workers (~100,000 workers), indicated that no excess cancer risk were observed in these studies when exposures to nickel in the inhalable aerosol fraction were kept ≤0.1 mg Ni/m^3 (Oller et al. 2014). The ability of nickel substances to induce respiratory tumors after inhalation may be related to the bioavailability of the Ni2+ ions at target sites within epithelial cells. The bioavailability of Ni2+ ions in the nucleus of target respiratory epithelial cells is not dictated by just the water solubility of the nickel particle but by the interplay of factors like respiratory toxicity, extracellular and intracellular dissolution, and lung clearance (Goodman et al. 2011).

Setting an OEL for inhalable nickel therefore at the of 0.01 mg/m3 provides a safety margin to protect against cancer and will reduce the risk from fibrosis and pneumoconiosis when exposed to respirable nickel.

Pneumoconiosis / fibrosis

Pulmonary changes such as fibrosis and pneumoconiosis have been reported in workers inhaling nickel dust. Airway hypersensitivity and asthma have been reported for some workers in the nickel-plating industry (Kolberg et al., 2020; Warshaw et al., 2019; Wittczak et al., 2012).

Other respiratory effects of the chronic inhalation of nickel can include hypertrophic rhinitis and sinusitis, the formation of nasal polyps, and perforations of the nasal septum (Bolek et al., 2017).

Berge and Skyberg (2003) analyzed radiographs of 1046 workers in a nickel refinery in Norway, according to the ILO standards. Pulmonary fibrosis (PF) was defined as a reading of ILO score ≥1/0 and following this criterion, 47 cases (4.5%) were identified. In logistic regression models, controlling for age and smoking, there was evidence of increased risk of PF with cumulative exposure to soluble nickel or sulfidic nickel ($p = 0.04$ for both).

Logistic regression models with cumulative exposure to one nickel species at a time, predicted a 10% (soluble Ni) or 15% (sulfidic Ni) increase in the prevalence of ILO score > 1/0 per 1 mg/m3 –year. With a sampler correction factor the reported average exposure time of 21.8 years, the 75th percentile cumulative exposure levels corresponded to average exposure levels of 0.17 and 0.6 mg/m3 for soluble and sulfidic Ni, respectively. Although it is noted that an ILO profusion score of > 1/0 does not necessarily correlate with clinical (or histopathological) diagnosis of lung fibrosis.

The incidence and severity of chronic lung inflammation (chronic active inflammation, alveolar proteinosis, and fibrosis), also after 2-years (NTP 1996b, 1996c) of inhalation exposure to 0.11 mg Ni/m3 nickel sub sulfide, were similar to, those observed with 0.11 mg Ni/m3 of nickel sulfate in rats based on 100 animals per group.

In the chronic nickel sulfate study rats were exposed to the lower exposure level 0.06 to 0.03 mg Ni/m^3, resulting in a significant decrease in incidence and severity of lesions to background inflammation levels.

A similar steep dose-response for inflammation is expected for nickel sub sulfide, based on results from 13-week studies.

For the soluble nickel sulphate hexahydrate, a Lowest Observed Adverse Effect Concentration (LOAEC) for chronic lung inflammation and fibrosis could be determined at 0.06 mg Ni/m^3, and a definitive No Observed Adverse Effect Concentration (NOAEC) for these effects could be set at 0.03 mg Ni/m^3 in the 2-years study.

Inflammatory reactions including fibrosis were also seen with poorly soluble nickel subsulphide (NTP 1996b) at 0.11 mg Ni/m3 and with nickel oxide (NTP 1996a) at 0.5 mg Ni/m^3 and, in form of alveolar proteinosis, alveolar histocytosis and chronic inflammation with metallic nickel at 0.1 mg/m^3. In all three cases this was the lowest concentration applied and no NOAEC could be identified. SCOEL argued that due to the severe lung damage or chronic inflammation observed at these concentrations, the 2-3-fold higher deposition of nickel after exposure to nickel oxide in humans (as compared in rats) and the estimated longer retention half-times in humans for Ni3S2 and NiO (Oller and Oberdoerster 2014), an OEL of 0.005 mg/m^3 (respirable fraction) was proposed for poorly soluble nickel compounds and metallic nickel.

The importance in particle size for deriving occupational exposure limits

NiPERA Inc. is the Nickel Institute's independently incorporated science division. NiPERA is also leading the way when it comes to particle size characterization and toxicity exerted based on particle size. The respirable exposure limit was derived by calculating the Human Equivalent Concentration (HEC) from chronic rat data. NiPERA explained that long-term respiratory (local) effects associated with inhalation exposures to nickel substances are considered related to the amount of nickel lung burden in the corresponding region of the respiratory tract. Lung inflammation and fibrosis were expected to be related to the retained nickel doses in the alveolar region, while lung tumours were related to the retained doses in trachea-bronchial and alveolar regions.

For the inhalable Derived No Effect Level (DNEL) NIPERA considered 13 cohorts (> 100,000 workers) and exposure data reported in terms of inhalable aerosol fraction. In this calculation the exposures were converted to inhalable equivalents (37 mm sampler to inhalable sampler, factor 2) as described in Oller et al (2014) and Goodman et al (2011). Dosimetric adjustments were applied to the animal toxicity values for each group of nickel substances calculating HECs to animal exposure by considering workplace particle size distribution (PSD). NiPERA noted that restricting inhalable nickel exposures to levels that prevent lung tumours is also expected to prevent nasal tumours. NiPERA therefore proposed inhalable DNELs of 0.05 mg Ni/m^3 for all nickel compounds and nickel metal, respectively based on respiratory cancer effects (not for nickel metal) in humans, supported by animal data and respiratory toxicity effects base on animal data supported by human data.

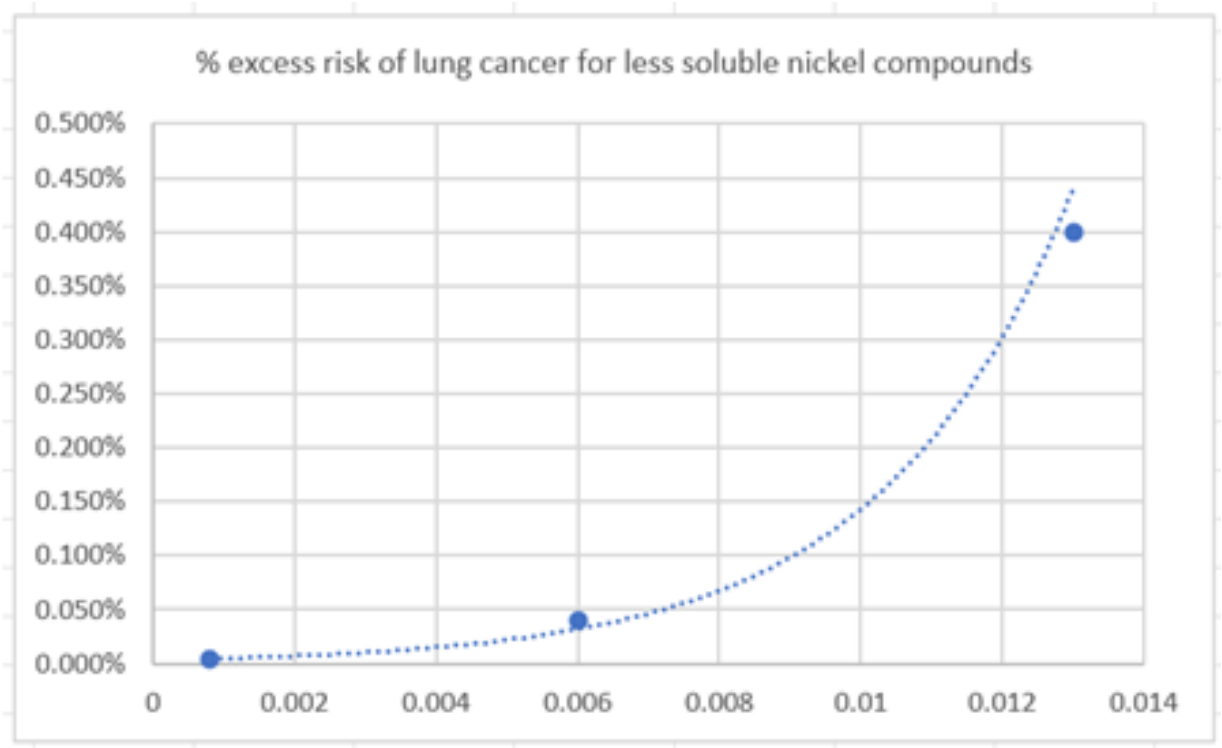
Analyses of dose-responses for the main chemical forms of nickel (soluble, oxidic and sulfidic compounds) that included 13 cohorts of nickel workers (~100,000 workers), indicated that no excess cancer risk were observed in these studies when exposures to nickel in the inhalable aerosol fraction were kept ≤ 0.1 mg Ni/m^3 (Oller et al. 2014).

NiPERA stated further that **"neither"** the **inhalable DNELs of 0.05 mg Ni/m^3** for all nickel compounds and nickel metal nor the **respirable guidance value of 0.01 mg Ni/m^3** were derived based on effects of nanoparticles (ECHA 2018).

Therefore, when setting a TLV®-TWA for nickel for both inhalable and respirable nickel compounds and metal, it is recommended that caveat be provided where the TLV®-TWA has not considered nickel metal / nickel compounds with a particle size < 100 µm (ECHA 2018, NiPERA 2017).

Would the ACGIH consider setting a separate TLV®-TWA for nickel at a particle size < 100 µm?

Inhalable DNELs of 0.05 mg Ni/m^3 for all nickel compounds and nickel metal, respectively was proposed based on respiratory cancer effects (not for nickel metal) in humans and supported by animal data and respiratory toxicity effects base on animal data supported by human data (NiPERA, ECHA 2018). The **respirable guidance** value of 0.01 mg Ni/m^3 for nickel metal and nickel compounds was derived by calculating HECs, derived from the animal data by using full dosimetry adjustments and for each group of nickel substances. Also nickel specific data for clearance rates and updated values for respiratory tract surface area in rats were considered (NiPERA, ECHA 2018). Derived exposure risk relationship for less soluble nickel compounds (Begründung zu Nickelverbindungen in TRGS 910) based on a threshold for cytotoxicity in the rat lung converted into the HEC for **poorly soluble respirable nickel compounds** of 6 µg Ni / m^3 (equivalent to 0.006 mg/m^3) for an assumed excess cancer risk in humans at workplace of 4 in 10,000. Conversely 4 in 1000 is a HEC 13 µg Ni / m^3 (equivalent to 0.013 mg/m^3) (ECHA 2018).



% excess risk vs. exposure to respirable "less soluble" nickel compounds (Adapted from ECHA 2018).

Note – assigning a TLV®-TWA of 0.01mg/m^3 for both "inhalable" sparingly soluble and soluble nickel species should also protect against respirable nickel. For many processes respirable nickel will be less than the inhalable fraction, except for nickel fume (ie. welding).

Technical limitations of lowering the occupational exposure limits for nickel

Occupational exposure limits (OEL) are time weighted averages (TWA) representing an 8-hr shift and are sometimes defined as sharp boundaries that must not be exceeded (e.g., EU CAD, EU Carcinogens Directive, UK COSHH). The large variability in workplace exposure means that occasional high results occur even where the exposure is generally well controlled. One may think that as long as all measured exposures are < OEL, compliance will be demonstrated. This is not the case. In practice, the majority of the exposure measurements have to be much lower than the OEL for compliance to be demonstrated with any degree of confidence. For example, the estimated average needs to be 5 or 10-fold lower than the OEL, depending on the OEL value and the number of measurements.

An exposure profile must be derived from exposure measurements, to allow sound statistical analysis. Only then can accurate comparisons be made of exposures against the OEL. Of course, to do this the level of exposure must be measured well below the OEL. International standards require that the exposure be measured at concentrations ≤ one tenth, or 10% of the OEL.

The level that can reliably be measured, is commonly referred to as the limit of quantitation (LoQ), minimum reported value (MRV), or limit of reporting (LoR). This requirement is described in ISO 15202- 3 which states that the LoQ be no more than 0.1 or 10% of the OEL. BS EN 482:20126 requires that the measuring range of the procedure or instrument shall cover the concentration from 0.1 times to 2 times the OEL.

It is important that if an OEL for respirable nickel compounds were assigned as 0.005 mg/m^3 then the sampling and analytical should meet the above criteria.

Due to the limitations in analytical feasibility for setting an OEL at 0.005 mg/m^3 for respirable nickel it may be prudent to assign the one limit as 0.01 mg/m^3 for inhalable nickel which will also be protective for respirable nickel.

Biological monitoring

Biological monitoring of exposure should be considered as being complimentary to personal exposure monitoring. Biological monitoring should be carried out using a traffic light approach outlined in this document and for mixed (soluble and sparingly soluble species) and BEI of 10 ug/L in urine has been recommended in line with AIOH 2016 position paper " Nickel and its compounds – potential for occupational health issues" which is especially important when considering reproductive health effects and developmental toxicity.

Despite the major differences in elimination between different nickel compounds, evaluating exposures should be based on biological monitoring for urinary nickel, with air monitoring being complementary to identify where

additional controls are required. Biomonitoring studies in exposed workers and conducting intervention studies, have shown improvements of Ni excretion in urine (Beattie et al. 2017; Lehnart et al. 2014). These improvements most likely have occurred by making workers aware of their individual situations and by successfully implementing improved hygienic measures at the workplace.

A useful intervention study (model) involving stainless steel welders who are exposed to nickel and as part of the process has demonstrated significant reductions in exposure. Air monitoring and biological monitoring (BM) (nickel in urine) before and after improved controls including improvements to respiratory protection (to positive pressure) and localized exhaust ventilation demonstrated reductions in respirable nickel exposure from 0.08 mg/m3 (2008) to 0.003 mg/m^3 (2011) and 7.9 μg/ L (2008) to 3.1 μg/L for urinary nickel. The urinary nickel reduction was close to 3.0 μg/L which is the German Biological Workplace Reference Value (BAR) representing the ninety-fifth percentile in the general population (Lehnart et al. 2014).

With respect to soluble nickel (nickel sulphate) exposure, the use of biomonitoring has been used to assess exposure in the electroplating industry. The aim of the study by Beattie et al. 2017, was to investigate whether "repeat biological monitoring (BM)" over time could help to drive improvement in exposure to nickel. The study demonstrated positive correlations between hand contamination and BM results that show that dermal exposure is a significant factor (Beattie et al. 2017).

Biological monitoring of workplace exposure to poorly soluble Ni compounds is essential due to the potential carcinogenic effect of poorly soluble Ni compounds on the lung of exposed workers after inhalation. A background level of < 3 μg/L (DFG, SCOEL, 2011) can be based on the concentrations of Ni in urine from non-occupationally exposed persons. A target (action) BEI has been recommended as 5 μg/L for poorly/ insoluble nickel compounds and precautionary guideline value of 10 μg/L nickel in urine is recommended as being more or less equivalent to sparingly soluble nickel (Tommassen et al. 1999, AIOH 2016); above this may indicate work practices that are not best practice. Establishing a baseline using urinary nickel level can be used as a measure of control effectiveness for workplaces where inhalation, or skin contamination, hence inadvertent hand mouth contact and ingestion may be an issue (AIOH 2016).

Mean concentrations between about 1 – 5 μg/L and 95th percentiles up to 8 μg/L have been reported in the adult population depending on the geographic location (Kiilunen et al., 1987; Minoia et al. 1990; Nisse et al., 2017). In the late 1980s the range of urinary nickel concentrations were noted by Neiboer E (2001) for Sudbury (Ontario, Canada) residents between 0.3 – 7.6 μg/L. It is important therefore that any reference value, for nickel in urine, for non-exposed be taken from the general population for those living in the same general area such as that determined for Sudbury. A precautionary guideline value of 10 μg/L nickel in urine is recommended, as being more or less equivalent, to sparingly soluble airborne nickel (Tomassen et al. 1999); above this may indicate work practices that are not best practice. Establishing a baseline using urinary nickel level can be used as a measure of control effectiveness for workplaces where inhalation, or skin contamination, hence inadvertent hand mouth contact and ingestion may be an issue and drive continuous improvement (AIOH 2016).
The following has been adapted from Beattie et al. 2017 which has been applied to the use of biomonitoring to assess exposure (nickel sulphate) in the electroplating industry.

Interpretation of biological monitoring results using the "traffic light" system for soluble nickel.

Nickel (soluble) µmol/mol (µg/L)		
Red	> 100** (71)	BM exposures equivalent to Great Britain Workplace Exposure Limits (WEL) for inhalation exposure 0.1mg/m3 (8hrs). Collect further samples and check controls urgently.
Amber	23 – 100** (16 – 70)	BM results over guidance values Collect further samples and check results. Look for reasons and check controls.
Green	< 23 (≤ 15)**	BM results below guidance values. 90th percentile for HSL data.
Background level (95%)*	(3) 10 (7)**	SCOEL (2011) BM results within background levels (95%). Great Britain.

(Adapted from source: Beattie et al. 2017, p.53**). (Note *) Carry out risk assessment for pregnant / breastfeeding worker where background level is exceeded. Note: µmol/mol converted to µg/L by multiplying by 0.7143, refer to Beattie et al. 2017, p.48, where it is noted that 3 µg/l (= ~ 4.2 µmol/mol) - conversion for typical creatinine concentration.

A recent publication by Bogen et al. 2021, discusses a human biokinetic model for soluble nickel addressing inter-individual variation. Biological Exposure Action Levels (BEALs) can provide health-based reference values to evaluate measures obtained through urinary Ni biomonitoring programs to complement existing industrial hygiene air monitoring programs. This work will support establishing a BEI® for soluble nickel and is a valuable reference when deciding on a BEI® in addition to following the traffic light approach as suggested above.

Interpretation of biological monitoring results using the "traffic light" system for insoluble / sparingly soluble nickel.

Nickel (insoluble / sparingly soluble) µg/L		
Red	> 10	Based on AIOH (2016) (Appendix IV), precautionary guideline value. Results above this value indicate work practices that are not best practice. In addition, because the ACGIH (2001) have denoted insoluble nickel compounds as an A1 confirmed human carcinogen and the IARC (2012) have implicated insoluble nickel compounds as being carcinogenic exposures should be as low as reasonably achievable (ALARA).
Amber	5 - 10	Collect further samples and check results. Look for reasons and check controls.
Green	< 5*	As insoluble nickel is a confirmed human carcinogen and may cause cancer by inhalation (H350i) ongoing efforts should be made to reduce exposures ALARA through continuous improvement. *Refer to appendix V.*
Background level	3 0.3 – 7.6	SCOEL (2011) Mixed nickel species background range of nickel in urine for Sudbury residents (late 1980s) (Nieboer 2001).

(Note *) Carry out risk assessment for pregnant / breastfeeding worker where background level is exceeded.

More recently Joh et al. (2021) has been able to correlate loss of lung function with quartiles of blood nickel concentrations which provides useful direction when considering a biological exposure index (BEI) for nickel.

A Korean study was carried out to assess the dose-response relationship between environmental exposure to nickel and pulmonary function in the Korean general population aged 40 or older. Quartiles of blood nickel concentrations were significantly associated with markers of pulmonary function in Korean men, such as forced

expiratory volume in 1 second (FEV1) and forced expiratory flow 25–75% (FEF25–75%). Dose–response relationships were observed between blood nickel levels and these pulmonary function parameters (FEV1 and FEF25–75%) (Joh et al. 2021). This study provides useful information to further help refine a BEI based on pulmonary health effects.

When reviewing a BEI for nickel AIOH 2016, provides useful guidance in addition. There are currently no BEI® for nickel, although it is on the ACGIH 'Under Study' list. SCOEL (2011) have recommended a biological guidance value (BGV) of 3 µg/L in urine based on background levels in a working age population. As such, it is not health based or an indication of risk and can only be considered as a guideline value when assessing effectiveness of exposure controls such as personal protective equipment (PPE). There should be caution when applying the SCOEL biological guidance value as this has not considered a range of populations. A more realistic urinary nickel reference value has been proposed by Hoet et al (2013), which covers a range of countries and populations. They recommend an upper reference limit (URL) equivalent to a 97.5th percentile of nickel in urine for a general adult population of 6 µg/L. However, "mixed nickel species for Sudbury residents" have been reported between 0.3 – 7.6 µg / L. Tomassen et al (1999) determined an airborne equivalent correlation between external exposure levels of sparingly soluble nickel compounds and urinary levels of nickel, whereby 0.1 mg/m3 exposure was equivalent to 10 µg /L in urine. This provides a rationale for assigning a BEI® of 10 µg /L in urine in addition to following the traffic light approach as discussed.

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Date Submitted: May 31, 2022

Chemical Substance **Welding Fumes**
(8 pages + citable materials)

Name of Group/Individual Submitting Comments: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
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Executive Summary *(limit 250 words)*

There are many workers globally who are exposed directly and indirectly to welding fumes. According to an estimate there are 11 million welders in the world and approximately 1 million in North America. This may be an underestimate since many countries do not have a robust human resource database and indirectly exposed workers' welding fume exposure is usually under reported.

The welding fumes exposure has wide range of adverse health effects reported in the scientific literature on respiratory, cardiovascular, and neurological systems. Moreover, it has been established that chronic exposure to welding fumes causes lung cancer and ocular melanoma.

Many countries have instituted 5 mg/m^3 PNOS exposure limit for welding fumes but it is too high to protect welders from its adverse health effects, therefore, it has been withdrawn in many cases. Due to its complex chemistry and wide range of exposure scenarios it is difficult to determine a TLV® that can encompass all the scenarios and protect from all the adverse health effects. However, due to its vast and deep impact on welders' health, it is imperative that a TLV® is established.

OHCOW recommends a two-prong strategy:

1) A TLV®-TWA of 0.1 mg/m^3 (respirable) be established to protect welders from welding fumes' non-cancerous health effects such as asthma, COPD, respiratory irritation, and neurological symptoms, except for stainless-steel welding and welding with beryllium.

2) In case of stainless-steel welding fume, the current TLV®s for hexavalent chromium and nickel should be used. In cases where beryllium exposure is suspected, the current beryllium TLV® should be used.

Chemical Substance: Welding Fumes

Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**

Specific Action Requested

1. It is recommended that the ACGIH® TLV®-TWA be 0.1 mg/m^3 for welding fumes in general, except stainless steel welding fumes and when beryllium is suspected in the welding fumes.
2. When stainless steel welding is done, users should be directed to use nickel and hexavalent chromium TLV®s. When beryllium is suspected in the welding fume, users should be directed to use the beryllium TLV®.

Rationale

Introduction

The welding fume exposure causes wide range of adverse health effects (to name a few asthma, COPD, pneumoconiosis) including lung cancer due to its complex and wide range of chemical composition. The welding fumes composition can be classified into different kinds of metals, gases, and particulates, the levels of which depends on the type of welding, base metal, coating on the welding surface, composition of the electrode, and other work practices factors such as the rate and the length of a weld etc.[1]

According to CAREX there were 330,000 welders in Canada in 2016 mainly in manufacturing and metal fabrication, construction, automotive repair and maintenance, and architectural and structural metals manufacturing. The welders are also categorized according to their intensity of their welding fume exposure into low (12% of the welders), medium (32% of the welders), and high (56% of the welders). Moreover, welding fume exposure and welding lead to 310 lung cancer and 15 ocular melanomas each year in Canada respectively, based on retrospective exposures from 1961-2001. This amounts to 1.3% lung cancer cases and 5.4% of ocular melanomas diagnosed annually. The lung cancers attributed to welding fumes costed $308 million in 2011.[2] It is estimated that there are 11 million welders worldwide and 110 million workers who are indirectly exposed to welding fumes.[3] In USA, there is also a large workforce of 754,000 who is employed as a full-time welder in 2021.[4]

Many countries have implemented an exposure limit of 5 mg/m^3 PNOS to control the welding fume exposure. However, this limit seems to be too high in the light of new scientific evidence. Therefore, some countries have withdrawn this exposure limit. The Netherlands' exposure limit of 1 mg/m^3 is case in point which has been reduced from 5 mg/m^3 (GESTIS limit values database GESTIS International Limit Values (dguv.de)). The PNOS exposure limit has been used historically for substances where clear scientific evidence or a dose response relationship is not available. However, a more rigorous approach should be taken when dealing with a confirmed carcinogen such as welding fume. Keeping in mind the welding fumes exposure's sever health outcomes it is imperative that a strategy is developed to lower the welders' exposure to welding fumes. Therefore, we are trying through this submission to gather some of the main scientific studies which can be helpful in determining a TLV®.

Welding fume related adverse health effects

Korczynski, R. (2000), studied the occupational health concerns of the welders in 8 companies initiated by the Workplace Safety and Health Branch of the provincial government of Manitoba, Canada. The study was initiated in response to the welders' complaints about the excessive welding fumes at their workplaces and adverse health effects from welding fume exposure such as welders' flash, sore/red/teary eyes, headaches, nosebleeds, and a black mucus discharge from their nasal discharge. Different hazards of welding fume such as iron oxide, manganese, ozone, carbon monoxide, and noise were measured, and exceedances were reported for all of them as compared with ACGIH TLV®s. It is found that the welders had high incidence of bronchitis and pneumonia as

compared with non-welders. Welders in general also has more work-related symptoms of chronic rhinitis, cough, phlegm, wheeze, chest tightness, dyspnea, pleurisy than non-welders.[5]

Antonini, J. (2003), conducted a literature review of epidemiological studies on welding fume related health effects. It is concluded in the study that it is difficult to compare the epidemiological studies due to vast variations in the exposure variables, however, large number of welders experience bronchitis, airway irritation, lung function changes, and a possible increase in the lung cancer.[6]

Toren et al (2020), studied invasive pneumococcal disease (IPD) in a population-based case control study to further the knowledge of metal fume exposure and the incidence of pneumonia. 4438 cases were selected in the age bracket of 20-65 from a Swedish registry of invasive infection caused by streptococcus pneumoniae. A Job Exposure Matrix is used to characterize the metal exposure. The welders showed an increased risk of IPD with an Odds ratio of 2.99 (95% CI 2.09 to 4.30).[7]

Grahn et al (2021), conducted a population-based cohort study from the Stockholm Public health survey from 2002, 2006, 2010, followed up until 2014 to study the Chronic Obstructive Pulmonary disease (COPD) among different professionals by linking the data with a Job Exposure Matrix (JEM). It is concluded that a positive exposure response relationship was found between particles (respirable crystalline silica, gypsum and insulation material, diesel exhaust, asphalt/bitumen, and welding fume) and COPD. Welding fume had a Hazard Ratio (HR) of 1.57 (CI 1.12-2.21).[8]

Toren et al (1999), studied onset of asthma in different professions in a nested case referent study. A random population sample of 15813 people between the ages of 21 to 51 years were selected and the information about their occupational exposure and asthma diagnosis were obtained through questionnaire survey. The odds ratio for welding fume causing physician diagnosed asthma was 1.6 (CI 1.1-2.6). It is concluded that the study indicates that the acrylate-based compounds and welding fume exposure are associated with adult onset of astma.[9]
Karjalainen et al (2002), performed a population-based study to learn the risk of asthma in different professions from the entire workforce of Finland. A total of 49575 cases of medically diagnosed asthma in the age range of 25-59 years were selected with onset of asthma within 1986-1998. 275 non administrative professions were studied to calculate the relative risk of acquiring asthma. A relative risk of 1.91 (1.71-2.14) was found among 395 male welders. 23 women were also found with a RR of 1.6 (1.06-2.41).[10]

Kendzia et al (2013), pooled 16 case control studies to calculate an odds of lung cancer among welders. The studies were from different countries including Canada, China, New Zealand, ad Europe from 1985-2010. A total of 15483 cases of lung cancer and 18388 controls were selected who performed welding on regular basis and as part time or on occasional basis. The OR for regular workers who ever performed welding was 1.44 (95% CI: 1.25-1.67) and for part time welders the OR was also elevated (OR=1.27, CI: 1.10-1.28) but not as much as regular welders.[11]

Ibfelt et al (2015), studied 9 different cardiovascular conditions among welders. The cohort was followed from 1986 to 2006. The study concluded that the particulates from welding fume increases the risk of cardiovascular diseases.[17]

Lung cancer risk from welding fume exposure

Honaryar et al (2019), performed a meta-analysis of 20 case-control studies and 25 cohort/nested case control studies to study the risk of lung cancer from welding fumes. The meta RR for cohort studies was 1.29 (CI: 1.2-1.39), 1.87 for case-control studies (CI: 1.53-2.29), and 1.17 for case-control studies adjusted for smoking and asbestos with a CI of 1.04-1.38. It is concluded in the study that the welding fumes increases the risk of lung cancer regardless of the type of steel welded, welding method, and independent of the presence of asbestos or tobacco smoking.[12]

International Agency for Research on Cancer (IARC) published a monograph volume 118 in 2017 in which they carried out an extensive evaluation of epidemiological evidence of welding fumes carcinogenicity. The IARC concluded that there is sufficient evidence in humans that the welding fumes causes lung cancer. A positive association between welding fume exposure and kidney cancer has also been found. Ther is also sufficient evidence for ocular cancer from ultraviolet radiation from welding operation. Furthermore, chronic exposure to welding fume has also been associated with asthma, brochitis, lung function changes, neurological disorders, and renal tubular dysfunction if cadmium is present.[3]

Cherrie & Levy (2020) evaluated some new evidence regarding welding fume's carcinogenic effect after IARC evaluation in 2017. The new evidence reinforces the earlier evidence that the welding fumes are carcinogenic without differentiating between stainless steel or mild steel welding fumes. The evidence for carcinogenicity is from welding fumes as total welding aerosols. The paper also suggests that the risk of lung cancer from welding fumes has been observed below 1 mg/m^3 or may be as low as 0.1 mg/m^3.[13]

Adverse health effects and welding fume exposure levels

Sjogren et al (2022), in a study entitled "An occupational exposure limit for welding fumes is urgently needed" suggest that the limit for welding fumes of 5 mg/m^3 which is used by many countries is not adequate to protect welders from its adverse health effects. Different studies are also summarized with welding fume exposure levels and their corresponding health effects. The range of exposure levels which can cause Ischemic Heart Disease, COPD, and preterm birth in pregnant women is 0.1-3.2 mg/m^3.[14,13]

Lillienberg et (2008), conducted a population-based study on welding fume exposure and respiratory health effects such as asthma, wheezing, and bronchitis. 316 males from 10 European countries were selected with a work history of welding at work including welders. The welding related work history was obtained through a questionnaire with questions on different variables of welding exposure and the frequency of exposure. The exposure levels were assigned to a particular welding activity and duration by the experts using the Netherland welding database comprised of 20 years of data. The exposures were divided into three tertiles and the lowest tertile of 0.02-0.31 mg/m^3 has a prevalence risk of 0.95 (95% CI 0.52-1.74) for asthma, 1.32 (95% CI 0.89-1.95) for wheeze, and 1.57 (95% CI 1.04-2.37) for bronchitis. Significant relation was found between bronchitis and welding fume exposure but not with asthma.[15]

Taj et al (2021), studied the effect of welding fume exposure on cardiovascular system in a six year longitudinal study. 78 mild steel welders and 98 controls were included in the study. The blood pressure and other markers of cardiovascular system were measured six years apart along with respirable dust in the breathing zone of the workers. Exposure to low to moderate respirable dust levels (0.5-0.7 mg/m^3) were associated with increased blood pressure.[16] In a similar study Gliga et al (2020), respirable dust at 0.5 mg/m^3 and manganese at 0.049 mg/m^3 in welding fumes are associated with changes in neurology related proteins in the blood serum. One of the proteins could be linked to Alzheimer's disease.[18]

Siew et al (2008), conducted a study to learn iron and welding fume exposure and the risk of lung cancer among Finnish men by using the Finnish Job Exposure Matrix. The relative risk for lowest welding fume category i.e., 0.1-10 mg/m^3 is 1.09 (95% CI 1.05-1.14) for all types of lung cancers. The highest welding exposure category of $\geq$ 50 mg/m^3 has highest RR of 1.15. These RR were adjusted for confounding exposures such as iron, nickel, and benzo(a)pyrene.[19]

Pesch et al (2019), studied the risk of lung cancer from exposure to welding fumes, nickel, and hexavalent chromium in two German case-control studies which were followed from 1988-1996. 3418 cases and 3488 controls were selected for the study and the information from their job specific questionnaire was linked to the respective measurements obtained from the worksites. An average welding fume exposure of $\leq$ 1.8 mg/m^3 showed increased risk of lung cancer independent of nickel and hexavalent chromium exposure; OR of 0.98 (95% CI 0.64-1.51) for less than 1 year exposure, OR of 1.41 (95% CI 0.73-2.75) for an exposure between 1-5 years, OR of 2.27 (95% CI 1.18-4.37) for more than 5 years of exposure.[20]
The wide range of welding fume exposure levels associated with different adverse health effects are summarized in the following table 1.

Table 1 Welding fume exposure levels for different adverse health effects

Study	**Health effect**	**Exposure level (mg/m^3)**
Cherrie & Levy (2020)	Lung cancer	0.1
Siew et al (2008)	Lung cancer	0.1-10
Pesch et al (2019)	Lung cancer	$\leq$ 1.8
Sjogren et al (2022)	IHD, COPD, Preterm and low weight birth	0.1-3.2
Lillenberg et al (2008)	Asthma, Bronchitis, Wheeze	0.02-0.31
Taj et al (2021)	Cardiovascular disease	0.5-0.7
Gilga et al (2020)	Neurology protein changes	0.5

The studies are comprised of cohort and case control studies with large sample sizes from different industrial sectors encompassing different welding techniques and materials. These studies do not mention if the measured welding fume levels are in respirable or inhalable size fractions. However, one can reasonably assume that they are in respirable size fraction since the major portion of a welding fume is in fine and ultrafine particulate size fraction. The particle size can be affected by the type of welding and the residual time, but the bulk of the particles would still be in the respirable size range.[21]

The large samples sizes in the studies mentioned in table 1 show the level of rigor in determining an exposure level linked to an adverse health effect. In other words, one we can be confident that if an exposure limit of 0.1 mg/m^3 respirable dust is set the workers' health will be protected from welding fumes respiratory, cardiovascular, and carcinogenic effect. However, it should be noted that a dose-response relationship between welding fume exposure and lung cancer has not been established, therefore, the suggested exposure limit should be used with caution. Perhaps a risk assessment should be carried out before welding and the exposure or welding constituents should be characterized. In case where a carcinogen is present in the fumes, for instance hexavalent chromium and nickel in stainless steel welding, the carcinogen's specific TLV® should be used to lower the exposure.

Beryllium which is also a carcinogen is present as an alloy in different metals and can be present in the welding fume as one of the constituents. It is found in different industries such as automotive, construction, electronics, aerospace, and defense. Although beryllium is present in the alloy or welding rod in a low concentration (as low as 0.0008%) but it can still be present in high concentration in the welding fume (> 2 $\mu g/m^3$).[22]

Conclusions

In summary, OHCOW recommends a TLV®-TWA of 0.1 mg/m^3 respirable dust for welding fumes in general with the exception of stainless steel and beryllium exposure. Current ACGIH TLV®s for hexavalent chromium and nickel should be used to control the welding fumes from stainless steel welding. Similarly, the current ACGIH TLV® for beryllium should be instituted when beryllium is suspected in the welding fumes.

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Date Submitted :May 31, 2022

Chemical Substance **Desflurane**
(7 pages + citable materials)

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Executive Summary *(limit 250 words)*

It is recommended that an ACGIH® TLV®-TWA be introduced at 8 ppm.

This recommendation is based on the studies by Souza et al (2016). In this study, anesthesiologists were matched to physicians not exposed to anesthesia in a case-control study. Matching was done to attempt to address confounders. The operating rooms underwent area sampling for anesthesia, while the anesthesiologists (cases) and non-exposed physicians (controls) underwent testing for biomarkers suggestive of cytotoxicity and genotoxicity. The anesthesiologists had at least 2 years' exposure to anesthesia and were exposed to halogenated anesthetic gases (specifically desflurane, isoflurane, or sevoflurane), although typically only to one halogenated anesthetic gas at a time. They were also exposed to nitrous oxide. When compared to the physicians without exposure to anesthesia, the anesthesiologists had a statistically significant negative change in cytotoxic and genotoxic effects. The mean exposure to desflurane was 16.4 ± 6.0 ppm, range 8.2 – 23.2 ppm. Although the anesthesiologists were also exposed to other anesthetic gases, it is reasonable to conclude it is possible that all could have an adverse effect.

Although this study is small and is unable to separate types of anesthetic gases from each other, it provides evidence of a potential exposure threshold for adverse health effects of desflurane. It is recommended that the lower end of the exposure range be adopted as the ACGIH® TLV®-TWA, rounded to the whole number of 8 ppm.

Chemical Substance: Desflurane

Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**

Specific Action Requested

1. It is recommended that an ACGIH® TLV®-TWA be introduced at 8 ppm. This recommendation is based on a study by Souza et al (2016). In this study, exposure to a mean of 16.4 ± 6.0 ppm (range 8.2 – 23.2 ppm) desflurane can result in evidence of genotoxic and cytotoxic effects in anesthesiologists with at least 2 years' exposure, compared to other physicians matched for age, sex, and lifestyle. Thus, it is recommended that the ACGIH® TLV® be set to below the range of exposure, rounded to the whole number of 8 ppm.

Rationale

Desflurane is a halogenated anesthetic gas that does not have an ACGIH® TLV®. It is approved by the US FDA for induction or maintenance of general anesthesia in adults, but in practice it is more often used for induction only (Khan and Liu 2021). It was first synthesized in the 1970s. It has a rapid onset, which is desirable in an anesthetic gas, but its higher cost results in it being used less frequently than other halogenated anesthetic gases (Meyer 2020). There is also a movement away from desflurane due to its higher greenhouse gas emissions compared to some other halogenated anesthetic gases (Gaya da Costa 2021).

When used as an anesthetic gas exposure may occur in the following ways in hospital, dental, or veterinarian surgical uses:

- When filling refillable vapourizers;
- During initial hookup;
- When checking the anesthesia system;
- From leaks in the anesthesia system;
- When checking the waste scavenging system;
- From leaks in the waste scavenging system;
- From an ineffective gas scavenging system;
- Escaping around patient's anesthesia mask, endotracheal tube, or laryngeal mask airway;
- During system flushing or purging at the end of surgery or procedure;
- During unintended spills;
- Exhalation of patients in post anesthesia care unit (PACU) or intensive care unit (ICU) (Korczynski et al 1999, McGregor et al 1999, Byhahn et al 2001, Herzog-Niescery et al 2019, Gaya da Costa 2021).

Desflurane is administered around 7.25% in those aged 18-30, and 6.0% in those aged 31-65 (Khan and Liu 2021). Desflurane is not typically used for induction of general anesthesia due to its odour. It is more commonly given for maintenance of general anesthesia (Khan and Liu 2021).

In an operating room with adequate ventilation and a functioning waste scavenger system, exposure to healthcare workers during surgery was highest in situations with poor air control, such as pediatric surgeries, and particularly pediatric surgeries during bronchoscopy (Byhahn et al 2001), dental surgeries (Cohen et al 1980) and veterinary surgeries (Korczynski et al 1999). An even greater potential for exposure occurs in the PACU and ICU when patients are exhaling waste anesthetic gases (Korczynski et al 1999, McGregor et al 1999, Byhahn et al 2001,Gaya da Costa 2021). PACU and ICU have lower ventilation requirements than procedure and operating rooms, and typically lack waste gas scavenger systems (Gaya da Costa 2021). Dental surgical exposures are typically 2- to 3-fold higher than hospital operating rooms (Cohen et al 1980).

Exposure in a laboratory setting will be dependent on the laboratory's standard operating procedures. Good laboratory safety practices will reduce the potential for exposures. The highest potential for exposure is with open containers of desflurane or desflurane solutions, including decanting, pouring, and otherwise transferring.

Exposure can occur in unintended spills. In both surgical and laboratory settings, strict spill responses are required. High exposure to desflurane can result in anesthetic effects.

Select occupational exposure limits are summarized in Table 1. It is noted that many jurisdictions do not have an occupational exposure limit for desflurane, nor is there an ACGIH® TLV®.

Table 1: Select Occupational Exposure Limits for Desflurane

Jurisdiction* (Year of Latest Update)	Limit (as described)	Limit Name
Denmark (2020)^	5 ppm / 35 mg/m^3	Grænseværdier (8-hour)
Finland (2020)	10 ppm / 70 mg/m^3 20 ppm / 140 mg/m^3	Haitallisiksi tunnetut pitoisuudet (8-hour) Haitallisiksi tunnetut pitoisuudet (15-minute)
NIOSH (2022)	2 ppm / 0.5 ppm if co-exposed to nitrous oxide	Recommended Exposure Limit (REL) for all waste halogenated anesthetic gases (60-minute Ceiling)
Norway (2022)^	5 ppm / 35 mg/m^3	Grenseverdier (8-hour)
Sweden (2021)	10 ppm / 70 mg/m^3 20 ppm / 140 mg/m^3	Nivågränsvärde (Level Limit Value) Korttidsgränsvärde (Short Term Limit Value)

* Refer to Citable Material List for each jurisdiction's citation.

^ The rationale for Norway's Limit (Norway 2010) is based on accepting the rationale for Denmark's Limit. The rationale for Denmark's Limit was not able to be reviewed prior to this submission.

Notably, while desflurane can be included with the waste halogenated anesthetic gas REL, the REL is not specifically for desflurane (NIOSH 1977). The most recent update refers only to a REL for waste halogenated anesthetic gases (NIOSH 2022).

In surgical and procedural suites, the use of scavenging systems and high ventilation flow result in low exposures. However, exposure can also occur when the anesthetized patient is exhaling anesthetic gases after the surgery. Monitoring has identified that occupational exposures tend to be higher in post anesthesia care units (sometimes called "recovery") and intensive care units, and lower in surgical and procedure suites. A select list of occupational exposure monitoring data is provided in Table 2. These values suggest that modern surgical and procedural suites can in fact achieve very low waste anesthetic gas exposures.

Table 2: Select Exposure Data to Desflurane

Location of Monitoring	Personnel Monitored	Exposure*	Study
Surgery (cardiopulmonary bypass (CPB))	Anesthesiologist, no scavenging	Median 0.90 ppm (0.56-6.08 ppm)	Hoeruf et al 1997
	Anesthesiologist, scavenging	Median 0.24 ppm (0.09-0.81 ppm)	
	Perfusionist, no scavenging	Median 0.93 ppm (0.54-6.10 ppm)	
	Perfusionist, scavenging	Median 0.26 ppm (0.10-0.79 ppm)	
Surgery (CPB)	Perfusionist	Mean 0.82 ± 0.26 ppm	Westphal et al 1997 (also reported by Byhahn et al 2001)
	Surgeon	Mean 0.62 ± 0.28 ppm	
Surgery (ophthalmic)	Anesthesiologist	Induction median 5.0 ppm (0.8-28.2 ppm)	Hobbhahn et al 1998
		Emergence median 2.57 ppm (0.05-15.4 ppm)	
		Overall median 0.47 ppm/hr (0.05-4.89 ppm/hr)	
	Nurse	Induction median 2.57 ppm (0.09-24.0 ppm)	
		Emergence median 2.08 ppm (0.05-22.6 ppm)	
		Overall median 0.48 ppm/hr (0.01-7.53) ppm/hr	
	Surgeon	Emergence median 1.57 ppm (0.1-12.2 ppm)	
		Overall median 0.43 ppm/hr (0.02-2.51 ppm/hr)	
Post anesthesia care unit (PACU)	Nurse	Mean 2.1 ± 1.2 ppm	Sessler and Badgwell 1998
Surgery (ophthalmic)	Anesthesiologist	Mean 0.43 ± 0.23 ppm	Byhahn et al 1999 (also reported by Byhahn et al 2001)
	Surgeon	Mean 2.80 ± 1.42 ppm	
Surgery (adult patient, ear-nose-throat)	Anesthesiologist	Mean 0.02 ± 0.03 ppm	Byhahn et al 2000
	Surgeon	Mean 0.21 ± 0.24 ppm	
Surgery (pediatric patient, ear-nose-throat)	Anesthesiologist	Mean 0.02 ± 0.03 ppm	
	Surgeon	Mean 0.30 ± 0.14 ppm	
Surgery (CPB)	Anesthesiologist, before CPB	Mean 0.02 ± 0.01 ppm	Mierdl et al 2003
	Anesthesiologist, on CPB	Mean 0.02 ± 0.003 ppm	
	Perfusionist, on CPB	Mean 0.82 ± 0.26 ppm	
	Surgeon, before CPB	Mean 0.21 ± 0.10 ppm	
	Surgeon, on CPB	Mean 0.62 ± 0.28 ppm	
PACU	Nurses	Mean 0.34 ppm (0.06-0.80 ppm)	Flack 2006
Surgery	Anesthesiologist	Mean 16.4 ± 6.0 ppm (8.2-23.2 ppm)	Souza et al 2016
Intensive Care Unit (ICU)	Area samples: in areas where nurse frequently works	Mean 0.65 ppm; Max 6.65 ppm	Herzog-Niescery et al 2019
PACU	Area samples: before staff did a hazard awareness module	Mean 0.25 ppm	Kampan 2019
	Area samples: after staff did a hazard awareness module	Mean 0.21 ppm	

* When exposure is presented with ± after, it refers to ± 1 Standard Deviation. When exposure is presented with (number range in brackets) after, the range in the brackets refers to the exposure range.

The study by Hobbhahn et al (1998) reported the overall median as ppm *per hour exposed* to reflect that monitoring was only done during surgery (induction, maintenance, emergence of patient being anesthetized). They

did not continue monitoring during breaks, which would have presumably had non-detectable exposure, making the TWA for the entire shift lower.

The NIOSH REL of 2 ppm was based on developing a REL that was the same as the limit of detection for sampling methodology of halogenated anesthetic gases. At that time (NIOSH 1977), 2 ppm was the limit of detection. This REL was selected based on the risk of spontaneous abortions in pregnant persons occupationally exposed to waste halogenated anesthetic gases, essentially embracing the "ALARA" (as low as reasonably achievable) principle. When exposed alone to a waste halogenated anesthetic gas, the REL is 2 ppm; but when exposed to a waste halogenated anesthetic gases + nitrous oxide at the same time, the waste halogenated anesthetic gas REL is 0.5 ppm (NIOSH 2022). Desflurane is often co-administered with nitrous dioxide.

Overall exposure of the measured exposures summarized in Table 2, when measured as either mean or median, was typically below 2 ppm. This is below the NIOSH REL when exposed to a waste halogenated anesthetic gases in the absence of nitrous oxide. However, the majority of these studies in fact involved the co-administration with nitrous oxide.

Adverse Health Effects

Desflurane is a newer halogenated anesthetic gas. Although it is well studied at levels that induce and are close to inducing anesthesia, less research was identified in the literature review of sub-anesthetic exposures than what was available for older anesthetic gases, such as enflurane or halothane. Desflurane. undergoes minimal biotransformation or metabolism before elimination (Edwards 1999, Stachnik 2006, Varughese and Ahmed 2021).

Desflurane is minimally metabolized, particularly when compared to older anesthetic gases, which means that less free fluoride is a produced. For these reasons, desflurane is hypothesized to not cause significant nephrotoxicity when used as an anesthetic (Reichle et al 2002, Stachnik 2006). Although this is referring to concentrations several orders of magnitude higher than occupational exposures to waste anesthetic gases, the same minimal metabolism would occur with occupational exposures, and so has a low risk of nephrotoxicity. In addition, it is hypothesized to also being a lower occupational hazard when compared to older anesthetics (Edwards 1999).

Desflurane is one-fifth as potent as isoflurane (Eger 1993, Hobbhahn et al 1998), one-eighth as potent as halothane (Eger 1993), and one-third as potent as sevoflurane (Eger 1993). However, potency does not translate to toxicity, and so would form only a crude estimation of relative risk when comparing occupational exposure limits.

Two reviews noted that there were no significant data into adverse occupational health effects from desflurane exposure (Byhahn et al 2001, Stachnik 2006).

Cytotoxic and Genotoxic Effects

A study of 26 medical residents in their first year of medical residency were monitored by Aun et al (2018). The residents were exposed to desflurane, isoflurane, sevoflurane, nitrous oxide. Typically, it is expected that only one halogenated anesthetic gas (desflurane, isoflurane, sevoflurane) would be used per case, and thus exposure would

only occur to one halogenated anesthetic gas. Blood samples were taken prior to entering residency, after 6 months of residency, and after 1 year of residency. The goal was to look for signs of DNA damage over the course of one year of exposure to waste anesthetic gases. No significant changes were identified in biomarkers of cytotoxicity or genotoxicity ($p > 0.05$). Based on these results, the authors conclude brief occupational exposure of up to 1 year of anesthetic gases, including desflurane, do not induce cytotoxicity or genotoxicity (Aun et al 2018).

An earlier study by same study group, published by Souza et al (2016) concluded that chronic exposure to desflurane, isoflurane, sevoflurane, and nitrous oxide resulted in changes to DNA damage if exposure was 2 years or longer. In this study, 27 anesthesiologists with at least 2 years' exposure to waste anesthetic gases were matched based on age, sex, and lifestyle, to 30 physicians without exposure to anesthesia. A key difference in this earlier study is that the exposed group was matched to an unexposed group (Souza et al 2016), as opposed to the more recent study in which each medical resident was their own control (Aun et al 2018)

Typically, exposure was to one halogenated anesthetic gas at a time, without multiple exposures during the same case (Souza et al 2016). Exposure was measured as follows:

Desflurane	16.4 ± 6.0 ppm (range 8.2 – 23.2 ppm)
Isoflurane	5.5 ± 4.4 ppm (range 0.4 – 16.5 ppm)
Sevoflurane	7.7 ± 8.7 ppm (range 0.2 – 34.4 ppm)
Nitrous oxide	150.3 ± 135.7 ppm (range 61.0 – 350.0 ppm)

Notes:

- Reported as mean
- ± refers to ± 1 Standard Deviation

This study has a noticeable limitation. The anesthesiologists were exposed to 4 anesthetic gases: nitrous oxide and the halogenated anesthetic gases of desflurane, isoflurane, and sevoflurane. As mentioned, there would be exposure to only one halogenated anesthetic gas per case. However, it is not possible to separate each anesthetic gas exposure to know if one anesthetic gas caused more damage than the others.

Although the group monitored was small (n=27), a statistically significant change was identified when measuring genotoxic and cytotoxic effects. Specifically, a difference was noted in the anesthesiologists having higher frequency of genotoxic and cytotoxic effects through the buccal micronucleas (MN) cytome (BMCyt) assay, karyorrhexis and pyknosis in lymphocytes by commet assay, and a lower frequency of basal cells, compared to the control group. The authors conclude exposure to halogenated anesthetic gases (desflurane, isoflurane, sevoflurane) and nitrous oxide results in genomic instability, cytotoxicity, and proliferative changes, detectable in those with at least 2 years' occupational exposure to anesthetic gases (Souza et al 2016).

Because both cases and controls were physicians with comparable levels of education and further matched for age, sex, and lifestyle; it is less likely that other confounding factors impacted these results. The main unknown is how much each anesthetic gas caused the health effects. Though, as noted, anesthetic gases all have similar, though not identical, health effects. Despite the limitations of this study, it provides an estimation using the ALARA principle for occupational exposure levels associated with adverse health effects.

Conclusions

It is noted, that in surgical and procedure suites that meet most current standards for air changes per hour and with a waste scavenging unit, surgery/procedure-long and shift-long exposures tend to be below 1 ppm (refer to Table 2). Of the 26 means/medians of multiple datasets reported, 23 datasets were below 1 ppm. The only extended duration of monitoring that was not below 1 ppm were as follows: nurses in PACU (mean 2.1 ppm), reported by Sessler and Badgwell (1998); ophthalmic surgeron (mean 2.8 ppm), reported by Byhahn et al (1999); and anesthesiologist (mean 16.4 ppm), reported by Souza et al (2016). Notably, the remaining 23 exposures (some studies reported means, some as medians; all representing multiple exposures) for the shift or procedure were all below 1 ppm. The only one of these studies that investigated adverse health effects was the study with the highest exposures (Souza et al 2016).

Exposure to desflurane 16.4 ± 6.0 ppm (range 8.2 – 23.2 ppm) may result in evidence of genotoxic and cytotoxic effects in anesthesiologists in those with a minimum of 2 years' exposure, compared to other physicians matched for age, sex, and lifestyle (Souza et al 2016). Although this case-control study was small, it demonstrated a statistically significant worsening of cytotoxic and genotoxic effects. The greatest criticism of this study is that no one participant was only exposed to one anesthetic gas, though this represents typical real-world occupational exposures for anesthesiologists in most parts of the world. It was also the only study found by this review that identified adverse health effects at subanesthetic, occupational exposure. Thus it is recommended that the ACGIH® TLV®-TWA be set at the lower end of the range of exposures identified by Souza et al (2016), rounded to the whole number of 8 ppm.

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Date Submitted: May 31, 2022

Chemical Substance **Enflurane**
(8 pages + citable materials)

Name of Group/Individual Submitting Comments: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
Authored by: Krista Thompson, MHSc, ROH, CRSP, Occupational Hygienist
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Executive Summary *(limit 250 words)*

It is recommended that the ACGIH® TLV®-TWA for enflurane be lowered to 0.8 ppm. This recommendation is based on the findings of the study by Lucchini et al (1995). This study compared those with both enflurane and nitrous oxide exposure, to controls. Controls were defined as either having had no anesthetic gas exposure or exposure to up to 55 ppm nitrous oxide.

A worsening of reaction time was statistically significantly when enflurane exposure was a mean of 1.3 ppm (range 0.1-7.6 ppm) combined with a mean exposure of nitrous oxide of 46 ppm (range 12-100 ppm), compared to controls. The worsening reaction time was not identified when enflurane exposure was a mean of 0.8 ppm (range 0.1-17.6 ppm) combined with a mean exposure of nitrous oxide of 63 ppm (range 7-100 ppm).

Exposure to enflurane and nitrous oxide are not the same in both exposure groups, making it hard to ascertain the effects of enflurane alone. But given some members of the control group had exposure to nitrous oxide up to 55 ppm, it likely due more to the effects of enflurane resulting in the increased reaction times. Further, sevoflurane is typically co-adminstered with nitrous oxide, making it impossible to separate the health effects.

Thus, there is a health-based adverse effect when exposed to 1.3 ppm enflurane but not 0.8 ppm enflurane. Therefore, a TLV®-TWA of 0.8 ppm is recommended.

Chemical Substance: Enflurane

Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**

Specific Action Requested

1. It is recommended that the ACGIH® TLV®-TWA be lowered to 0.8 ppm. This recommendation is based on the findings of the study published by Lucchini et al (1995).

Rationale

Enflurane is a halogenated anesthetic gas that is not widely used in most settings (Hudson et al 2013, Chung and Muzio 2021, Hoggard et al 2021) due to its slower action (Enflurane; in: Livertox). It was first synthesized in 1963 and was first used in the USA in 1972 (Halogenated Anesthetic Gases; in: Livertox). Enflurane has largely been replaced by other halogenated anesthetic gases, including isoflurane, sevoflurane, and desflurane. It is still used as part of a laboratory standard (Accorsi et al 2003), and it is still available for sale in North American (Millipore Sigma SDS No. 1235809).

When used as an anesthetic gas exposure may occur in the following ways in hospital, dental, or veterinarian surgical uses:

- When filling refillable vapourizers;
- During initial hookup;
- When checking the anesthesia system;
- From leaks in the anesthesia system;
- When checking the waste scavenging system;
- From leaks in the waste scavenging system;
- From an ineffective gas scavenging system;
- Escaping around patient's anesthesia mask, endotracheal tube, or laryngeal mask airway;
- During system flushing or purging at the end of surgery or procedure;
- During unintended spills;
- Exhalation of patients in post anesthesia care unit (PACU) or intensive care unit (ICU) (Korczynski et al 1999, McGregor et al 1999, Byhahn et al 2001, Gaya da Costa 2021).

The lungs absorb 35% of inhaled enflurane, while 2.5% is metabolized (Pezzagno et al 1989). Over 90% of anesthetic gases are eliminated unchanged, which highlights the importance of waste scavenger systems as an engineering control (Lahvic and Liu 2021). Modern surgical and procedural suites in hospitals typically have waste scavengers systems in wealthy nations.

In an operating room with adequate ventilation and a functioning waste scavenger system, exposure to healthcare workers during surgery was highest in situations with poor air control, such as pediatric surgeries, and particularly pediatric surgeries during bronchoscopy (Byhahn et al 2001), dental surgeries (Cohen et al 1980) and veterinary

surgeries (Korczynski et al 1999). An even greater potential for exposure occurs in the PACU and ICU when patients are exhaling waste anesthetic gases (Korczynski et al 1999, McGregor et al 1999, Byhahn et al 2001, Gaya da Costa 2021). PACU and ICU have lower ventilation requirements than procedure and operating rooms, and typically lack waste gas scavenger systems (Gaya da Costa 2021). Dental surgical exposures are typically 2- to 3-fold higher than hospital surgical exposures (Cohen et al 1980).

Exposure in a laboratory setting will be dependent on the laboratory's standard operating procedures. Good laboratory safety practices will reduce the potential for exposures. The highest potential for exposure is with open containers of enflurane or enflurane solutions, including decanting, pouring, and otherwise transferring.

Exposure can occur in unintended spills. In both surgical and laboratory settings, strict spill responses are required. High exposure to enflurane can result in anesthetic effects.

An environmental scan of select settings identified that occupational exposure limits for enflurane vary widely, from 0.3-153 ppm. A select list of occupational exposure limits is summarized in Table 1.

Table 1: Select Occupational Exposure Limits for Enflurane

Jurisdiction* (Year of Latest Update)	Limit (as described)	Limit Name
ACGIH® (2021)	75 ppm	TLV®- TWA
Australia (2019)	0.5 ppm / 3.8 mg/m^3	TWA for 8-hours/day or 5-days/week
Canada – Federal (2022)	75 ppm	Adopted TLV®-TWA
Canada – British Columbia (2022)	2 ppm	8-hour TWA
Canada – Ontario (2020)	2 ppm / 16 mg/m^3	TWA Limit
Denmark (2020)	2 ppm / 15 mg/m^3	Grænseværdier (8-hour)
Finland (2020)	10 ppm / 77 mg/m^3 20 ppm / 150 mg/m^3	Haitallisiksi tunnetut pitoisuudet (8-hour) Haitallisiksi tunnetut pitoisuudet (15-minute)
Germany (2021)	20 ppm / 150 mg/m^3	Maximale Arbeitsplatzkonzentration (MAK)
Netherlands (2021)	153 mg/m^3	Grenswaarde (8-hour)
NIOSH (2022, originally 1977)	2 ppm / 0.5 ppm if co-exposed to nitrous oxide	Recommended Exposure Limit (REL) for all waste halogenated anesthetic gases (60-minute Ceiling)
Norway (2022)	0.3 ppm / 2.3 mg/m^3	Grenseverdier (8-hour)
Sweden (2021)	10 ppm / 80 mg/m^3 20 ppm / 150 mg/m^3	Nivågränsvärde (Level Limit Value) Korttidsgränsvärde (Short Term Limit Value)
United Kingdom (2020)	50 ppm / 383 mg/m^3	Workplace Exposure Limit (WEL) (8-hour)

*Refer to Citable Material List for each jurisdiction's citation.

Most research on enflurane is either focussed on the health effects to the intentionally anesthetized patient or animal, or on the deleterious environmental effects.

A select list of occupational exposure monitoring is provided in Table 2. This included monitoring in both unscavenged rooms and scavenged rooms, as reported by Sass-Kortsak et al (1981), though the more recent studies were in rooms with waste scavenging. These two studies confirmed that waste scavenger systems reduce exposure to enflurane. As noted previously, waste scavenger systems are an engineering control.

Table 2: Select Exposure Data to Enflurane

Location of Monitoring	Personnel Monitored	Mean Exposure (Range)	Study
Unscavenged rooms	Area: general room	1.29 ppm (0.18-3.27 ppm)	Sass-Kortsak et al 1981
	Area: near anaesthesia unit	2.36 ppm (0.1-5.16 ppm)	
Scavenged rooms	Area: general room	0.25 ppm (<0.003-1.13 ppm)	
	Area: near anaesthesia unit	0.41 ppm (<0.003-2.16 ppm)	
Operating Room	Anesthetists, Surgeons, Nurses	1.3 ppm (0.3-8 ppm)	Imbriani et al 1994
Operating Room	Nurses – beginning of week	0.8 ppm (0.1-7.6 ppm)	Lucchini et al 1995
Operating Room	Nurses – end of week	1.3 ppm (0.1-18.8 ppm)	Lucchini et al 1995
Operating Room	Surgeons	0.25 ppm	Hoerauf et al 1996
Operating Room	Anesthetists	0.34 ppm	Hoerauf et al 1996
Operating Room	Nurses	0.57 ppm	Hoerauf et al 1996

There was no published occupational exposure monitoring in the dental sector, nor the veterinary sector identified in the literature review for this submission by OHCOW. Nitrous oxide is more often used alone in dental anesthesia than with halogenated anesthetic gases (Boiano et al 2017). In the past, enflurane was used in some dental anesthesia. It is probable that exposure to enflurane was higher than hospital-based surgical exposures because dental hygienists and dental assistants do not consistently check for leaks in waste anesthetic gas scavenging systems (Boiano et al 2017). Waste anesthetic gas scavenging systems, combined with adequate general ventilation, are important control measures to reduce exposure.

Veterinary anesthesia also uses halogenated anesthetic gases. Though enflurane was used in the past, it is not commonly used now (Korczynski et al 1999). Veterinary use of halogenated anesthetic gases results in higher exposures due to leakage from imperfect fitting masks around animals (Korczynski et al 1999). A review concluded that waste anesthetic gas scavenging systems are important control measures in veterinary medicine (Smith 1993).

Neurological Effects

A 1975 study compared performance on psychological tests before-and-after four hours' exposure to one or two anesthetic gases (Bruce and Bach 1975). The participants were exposed to either 500 ppm nitrous oxide alone, or to 500 ppm nitrous oxide with 15 ppm enflurane. The tests were also repeated before-and-after inhaling regular air for four hours. Importantly, the participants reported they could not detect if they were receiving air or anesthetic gas. Each participant had the psychological tests done before and after four hours' inhalation.

The mean reaction time had a statistically significant increase after administration of enflurane and nitrous oxide ($p<0.005$). The tests were done twice in those who breathed just air to detect and compare to a "practice effect" for reference. For the mean reaction time, it was expected that reaction time would improve (decrease in reaction time), which was in fact what happened. When given just nitrous oxide, the mean reaction time also improved (decreased in reaction time). Thus only 15 ppm enflurane (given with nitrous oxide) reduced reaction time.

The study was performed after anesthesia stopped being administered, so the participants were breathing normal air again. The authors note this is a limitation, and they further conclude that the results would likely have been more impaired if done while the anesthesia was being administered. It is clear that exposure to 15 ppm enflurane

results in a statistically significant reduction in reaction time after even after enflurane administration stopped. Although this study was included in the past ACGIH® enflurane review (ACGIH 2001), it did not result in a TLV®-TWA of 15 ppm.

A 1995 Italian study that compared occupational exposure to nitrous oxide and enflurane before and after shifts in 62 surgical nurses and 46 nurses as controls (Lucchini et al 1995). Notably, this study was not referenced in the past ACGIH® enflurane review (ACGIH 2001). In this study, nurses exposed to enflurane + nitrous oxide were compared to controls. The controls included those who were not exposed to any anesthetic gases as well as those exposed to up to 55 ppm nitrous oxide without any halogenated anesthetic gas exposure. Occupational exposure monitoring was done twice for the exposed workers: at the beginning of the week and again at the end of the week.

In the beginning-of-week monitoring, the mean exposure to enflurane was 0.8 ppm (range 0.1-7.6 ppm) and the mean exposure to nitrous oxide was 45 ppm (range 12-333 ppm). In the end-of-week monitoring, the mean exposure to enflurane was 1.3 ppm (range 0.1-18.8 ppm) and the mean exposure to nitrous oxide was 62.6 ppm (7-553 ppm). The nurses completed neuropsychological and response time tests and compared to the control group (unexposed + nitrous oxide-exposed nurses). In the exposed group, results were excluded if nitrous oxide exposure exceeded 100 ppm. In the control group, exposure to nitrous oxide up to 55 ppm were included, though as noted some controls also had no nitrous oxide exposure.

There was a statistically significant reduction in performance in the simple response time tests in the end-of-week exposed group with a mean of 1.3 ppm exposure to enflurane + mean of 62.6 ppm exposure to nitrous oxide ($p=0.015$) when compared to the control group. There was no reduction in the simple response time times in the beginning-of-week group with exposure to a mean of 0.8 ppm enflurane + mean of 45 ppm exposure to nitrous oxide when compared to the control group.

The authors conclude that short-term exposures to nitrous oxide and enflurane below the occupational exposure limits at the time cause reversible impairments. The impact of nitrous oxide is hard to separate from enflurane alone. That said, exposure to enflurane is typically occurring simultaneously to nitrous oxide. The combined exposure to enflurane and nitrous oxide may have an additive or supra-additive effect in the exposed group, but it is unknown which. That said, the control group included some individuals with nitrous oxide exposure. It can be concluded that this data provides evidence of adverse health effects at 1.3 ppm enflurane, with no health effects at 0.8 ppm enflurane, and unknown impacts from nitrous oxide. Enflurane and nitrous oxide are typically co-administered as anesthesia, making it the norm that occupational exposure would occur to both simultaneously.

Spontaneous Abortion

There are many studies investigating the risk of spontaneous abortion in female healthcare workers and wives of male healthcare workers exposed to anesthetic gases published. Due to the many studies produced, this document is focussed on two meta-analyses and three reviews to investigate if primary sources were required.

A meta-analysis of 19 studies investigating female healthcare workers exposed to anesthetic gases and spontaneous abortion calculated a relative risk (RR) of all studies of 1.48 (95%CI 1.4-1.58). The studies included

in the analysis were all studies published between 1971-1987 without any consideration or exclusion based on quality of study (Boivin 1997). A more recent meta-analysis of 15 studies with more strict criteria investigated the association between anesthetic gas exposure in healthcare workers and spontaneous abortion published between 1971-1995 (Quansah and Jaakkola 2010). Using a random effects model, the summary odds ratio for spontaneous abortion was 1.27 (95%CI 0.99-1.63). The studies in both meta-analyses included exposure to nitrous oxide. Nitrous oxide is associated with increased risk of spontaneous abortion at levels much higher than the current occupational exposure limits. Therefore, the results are different to attribute to enflurane. In addition, in the 1970s, exposures were very commonly much higher than the current occupational exposure limits, further complicating how much can be attributed to enflurane. A questionnaire-based study noted an increased risk of spontaneous abortion in dental hygienists exposed to nitrous oxide without waste scavenging systems compared to those exposed with waste scavenging systems (Rowland et al 1995), suggesting but not confirming the risk may be due to nitrous oxide exposure.

It is possible that the anesthetic gas of concern was actually nitrous oxide, or it is possible that the poor quality of the studies including enflurane make it difficult to assess the risk. The reviews are turned to for greater interpretation than the details identified in the scan of primary literature. A 2006 review concluded the poor design and lack of quality of past studies investigating risk of spontaneous abortion indicates that no conclusions can be drawn from these studies (Stachnik 2006). A systemic review of occupational exposure concluded that there was no consensus on the risk of spontaneous abortion, though the authors noted they did not consider or compare any consensus between lower and higher quality studies (Molina Aragonés et al 2016).

Animal models also need to be considered. There have been many animal studies using anesthetic gases. Two reviews have noted there have been many animal studies investigating reproductive effects, including mating behaviour, fertility, embryonic and fetal wasting, development of congenital abnormalities, and postnatal behaviour. The reviews both concluded that the enflurane did not have any reproductive effects in animal models at concentrations that are equivalent to much higher than waste anesthetic gas occupational exposures (McGregor 2000, Stachnik 2006). It was due to these reviews' conclusions that only a "literature scan" of the primary literature was completed, without further investigation into risk of spontaneous abortion.

Systemic Sclerosis

Two case reports have been published, each noting an ansethesiologist exposed to anesthetic gases developed systemic sclerosis. In the first case report, an anesthesiologist exposed to very high levels of mixed anesthetic gases for years was diagnosed with systemic scelorosis, (Magnavita 2016). Exposure to all anesthetic gases was anticipated to be higher than current ACGIH® TLV®s, with combined halogenated anesthetic gas (desflurane, enflurane, isoflurane) estimated to be over 100 ppm based on occupational monitoring in a nearby hospital with similar conditions.

In the second case report, also with an anesthesiologist, identified that the anesthesiologist was exposed to mixed anesthetic gases, including enflurane, without a waste scavenging system. The anesthesiologist was diagnosed with systemic sclerosis (Magnavita et al 2020). In the absence of a waste scavenging system, exposures estimated by the authors were above the current ACGIH® TLV®-TWA.

Given the high exposure potential in both case reports, it is difficult to extrapolate conclusions to lower exposures that would be at or below the TLV®-TWA or NIOSH REL or other occupational exposure limits.

Renal Effects

Enflurane is not a renal toxin when used at anesthetic doses in those with normal renal function (Stachnik 2006). No literature was identified investigating renal effects in subanesthetic exposures, such as to waste anesthetic gases.

Long Term Health Effects

A systemic review of occupational exposure conducted by Molina Aragonés et al (2016) concluded that, as of the review date (January 2014), no studies had conclusively shown adverse effects of long-term exposure to enflurane.

Enflurane comparison to Isoflurane

Enflurane and isoflurane are isomers. Isoflurane is still in use (Hawkley et al 2021, Hoggard et al 2021), whereas enflurane is not widely used (Hudson et al 2013, Chung and Muzio 2021, Hoggard et al 2021). Enflurane has a TLV®-TWA of 75 ppm, whereas the isomer isoflurane has a TLV®-TWA of 50 ppm.

The amount of both halogenated anesthetic gases is similar for anesthesia. Enflurane is typically used from 1.5-4% (Enflurane; in: Livertox), though can be as low as 0.5% (Black 1979, Chung and Muzio 2021). Isoflurane is typically used from 0.5-3% (Isoflurane; in: Livertox), though it can be as given as high as 4% (Hawkley et al 2021). Thus, both have a range of 0.5-4%. Enflurane is slow to act, so it often given with another anesthetic gas for induction. Isoflurane is rarely given for induction due to its smell, but is used as maintenance.

Enflurane and isoflurane are isomers. OSHA reports enflurane and isoflurane have similar acute properties (OSHA 103). However, the amount metabolized in the liver is different: 2-5% enflurane is metabolized by the liver protein CYP 2E1 (Stachnik 2006), compared to 0.2% by isoflurane (Halogenated Anesthetic Gases; in: Livertox). Isoflurane undergoes minimal metabolism, whereas enflurane undergoes intermediate metabolism (Stachnik 2006). Neither is hepatotoxic when used at higher doses for short-term anesthesia (Hoggard et al 2021), but it was not clear if that was true of long-term exposure to waste anesthetic gases. Enflurane is linked to an increased risk of seizures when used as an anesthesia, particularly in pediatric populations and those prone to seizures (Hoggard et al 2021).

Enflurane comparison to Halothane

In the rationale for Norway's occupational exposure limit (Norway 2000), the health effects of enflurane are compared to a well-studied anesthetic gas called halothane. It is noted they have very similar health effects, but different absorptions. Halothane has 60% absorption while 20-46% is metabolized (Norway 2000). Enflurane is 35% absorbed (Pezzagno 1989) while 2.5% is metabolized (Pezzagno 1989, Kaminsky et al 1990).

The ratio of total absorption for halothane is thus approximately 12% (60% x 20%), using the lower absorption estimate cited (Norway 2000). The ratio of total absorption for enflurane is 0.875% (35% x 2.5%). Using is approximately 14-times less absorption of enflurane, compared to halothane.

The Norwegian Grenseverdier (occupational exposure limit) for halothane is 0.02 ppm. Using the ratio of 14-times higher, the Grenseverdier (occupational exposure limit) for enflurane is 0.02 ppm x 14, or approximately 0.3 ppm, rounded.

Conclusions

Enflurane is not widely used (Hudson et al 2013, Chung and Muzio 2021) due it being slower acting than other anesthetic gases (Enflurane; in: Livertox). When used as an anesthesia, it also increased the risk of seizures (Hoggard et al 2021).

Enflurane is documented to increase reaction times after four hours' inhaling 15 ppm plus nitrous oxide ($p<0.005$), but reaction times decreased when given just nitrous oxide or after breathing just air (Bruce and Bach 1975). In studies in surgeries of waste anesthetic gas exposures (Lucchini et al 1995), it was identified that reaction time was statistically significantly increased when the enflurane mean exposure was 1.3 ppm (range 0.1-18.8 ppm) plus mean nitrous oxide exposure 62.5 ppm when compared to a control group with either no anesthetic gas exposure or nitrous oxide exposure up to 55 ppm. Notably the increase in reaction times was not identified when the enflurane mean exposure was 0.8 ppm (range 0.1-7.6 ppm) plus mean nitrous oxide exposure 45 ppm. In this study, it is harder to extrapolate an exposure threshold because there was a range of exposures in both groups. That said, enflurane is typically co-administered with nitrous oxide, so it will always be difficult to separate occupational exposures to enflurane from nitrous oxide. Thus, it is concluded that the mean of 0.8 ppm enflurane does not demonstrate adverse health effects.

Given enflurane and isoflurane are isomers, with very similar acute effects, and very similar pharmacological properties, there is an argument for the TLV®-TWAs to be the same. However, it is established that different isomers do not necessarily have identical health effects. Instead, the study by Lucchini et al (1995) provides a strong argument for a health-based TLV®-TWA of 0.8 ppm, as a threshold at which adverse health effects are not anticipated.

Therefore, it is recommended the TLV®-TWA of enflurane be lowered to 0.8 ppm.

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Date Submitted: May 31, 2022

Chemical Substance **Sevoflurane**
(10 pages + citable materials)

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Executive Summary *(limit 250 words)*

It is recommended that an ACGIH® TLV®-TWA be introduced at 0.2 ppm.

A threshold for adverse health effects was identified in the study by Souza et al (2016). In this study, anesthesiologists were matched to physicians not exposed to anesthesia. Exposure to at least 2 years to anesthetic gases (nitrous oxide, plus desflurane, isoflurane, or sevoflurane) resulted in statistically significant negative changes in cytotoxic and genotoxic health effects. The mean exposure to halogenated anesthetic gases was 9.9 ppm, but it varied by individual gas. Notably, exposure would have been to one halogenated anesthetic gas (desflurane, isoflurane, or sevoflurane) at a time. For sevoflurane, the mean was 7.7 ± 8.7 ppm, range 0.2 – 34.4 ppm. Although risks from each halogenated anesthetic gases + nitrous oxide are not able to be analyzed separately, it is reasonable to conclude it is possible that all would have an adverse effect.

Although this study is small and is unable to separate types of anesthetic gases from each other, it provides evidence of a potential exposure threshold for adverse health effects. It is recommended that the lower end of the exposure range be adopted as the ACGIH® TLV®-TWA, 0.2 ppm.

Chemical Substance: Sevoflurane

Contact Name: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*)**: Citations provided at end of document.**

Specific Action Requested

1. It is recommended that an ACGIH® TLV®-TWA be introduced at 0.2 ppm. This recommendation is based on a study by Souza et al (2016). In this study, exposure to a mean of 7.7 ± 8.7 ppm, range 0.2 – 34.4 ppm, sevoflurane can result in evidence of genotoxic and cytotoxic effects in anesthesiologists with at least 2 years' exposure, compared to other physicians, matched for age, sex, and lifestyle. Thus, it is recommended that the ACGIH® TLV® be set to below the range of exposures, at 0.2 ppm, as a very protective, evidence-based occupational exposure limit.

Rationale

Sevoflurane is a halogenated anesthetic gas that does not have an ACGIH® TLV®. In an American survey, sevoflurane was identified as the most common halogenated anesthetic gas, usually co-administered with nitrous oxide (Boiano and Steege 2016), so it is a useful agent to review.

Sevoflurane is used for induction and maintenance of anesthesia (Edgington et al 2021). It was first synthesized in 1968, and first approved for clinical use in 1990 in Japan, then later Great Britain in 1992, and the United States in 1995 (Smith et al 1996). It undergoes minimal hepatic metabolism (Edgington et al 2021). As with many other anesthetic gases, it is also used for sedation (Michel and Constantin 2009).

When used as an anesthetic gas exposure may occur in the following ways in hospital, dental, or veterinarian surgical uses:

- When filling refillable vapourizers;
- During initial hookup;
- When checking the anesthesia system;
- From leaks in the anesthesia system;
- When checking the waste scavenging system;
- From an ineffective waste gas scavenging system or from leaks in the waste gas scavenging system;
- Escaping around patient's anesthesia mask, endotracheal tube, or laryngeal mask airway;
- During system flushing or purging at the end of surgery or procedure;
- During spills;
- Exhalation of patients in post anesthesia care unit (PACU) or intensive care unit (ICU) (McGregor et al 1999, Byhahn et al 2001, Herzog- Niescery et al 2018, Gaya da Costa 2021).

Sevoflurane is administered at decreasing concentrations with increasing age, ranging from 3.3% (newborn to one-month-old full-term infants) to 1.4% (age 80 years) (Edginton et al 2021).

In an operating room with adequate ventilation and a functioning waste scavenger system, waste anesthetic gas

exposure to healthcare workers during surgery was highest in situations with poor air control, and particularly pediatric surgeries (Byhahn et al 2001, Herzog-Niescery et al 2017), dental surgeries (Cohen et al 1980, Kim and Kim 2021) and veterinary surgeries (Korczynski et al 1999, Oyama et al 2018). An even greater potential for exposure occurs in the PACU and ICU when patients are exhaling waste anesthetic gases (Korczynski et al 1999, McGregor et al 1999, Byhahn et al 2001, Gaya da Costa 2021). PACU and ICU have lower ventilation requirements than procedure and operating rooms, and typically lack waste gas scavenger systems (Gaya da Costa 2021). Dental surgical exposures are typically 2- to 3-fold higher than hospital surgical exposures (Cohen et al 1980, Kim and Kim 2021).

Exposure in a laboratory setting will be dependent on the laboratory's standard operating procedures. Good laboratory safety practices will reduce the potential for exposures. The highest potential for exposure is with open containers of sevoflurane or sevoflurane solutions, including decanting, pouring, and otherwise transferring.

Exposure can occur in unintended spills. In both surgical and laboratory settings, strict spill responses are required. High exposure to sevoflurane can result in anesthetic effects.

Select occupational exposure limits are summarized in Table 1. It is noted that many jurisdictions do not have an occupational exposure limit for sevoflurane, nor is there an ACGIH® TLV®.

Table 1: Select Occupational Exposure Limits for Sevoflurane

Jurisdiction* (Year of Latest Update)	Limit (as described)	Limit Name
Denmark (2020)	5 ppm / 42 mg/m^3	Grænseværdier (8-hour)
Finland (2020)	10 ppm / 83 mg/m^3 20 ppm / 170 mg/m^3	Haitallisiksi tunnetut pitoisuudet (8-hour) Haitallisiksi tunnetut pitoisuudet (15-minute)
NIOSH (2022)	2 ppm / 0.5 ppm if co-exposed to nitrous oxide	Recommended Exposure Limit (REL) for all waste halogenated anesthetic gases (60-minute Ceiling)
Norway (2022)^	5 ppm / 35 mg/m^3	Grenseverdier (8-hour)
Sweden (2021)	10 ppm / 80 mg/m^3 20 ppm / 170 mg/m^3	Nivågränsvärde (Level Limit Value) Korttidsgränsvärde (Short Term Limit Value)

* Refer to Citable Material List for each jurisdiction's citation.
^ The rationale for Norway's Limit (Norway 2010) is described as citing expert opinion but is not fully defined.

The NIOSH REL of 2 ppm was based on developing a REL that was the same as the limit of detection for sampling methodology of halogenated anesthetic gases. At that time (NIOSH 1977), 2 ppm was the limit of detection. This REL was selected based on the risk of spontaneous abortions in pregnant persons occupationally exposed to waste halogenated anesthetic gases, essentially embracing the "ALARA" (as low as reasonably achievable) principle. Notably this is a two-stage REL: when exposed alone to a waste halogenated anesthetic gas, the REL is 2 ppm; but when exposed to a waste halogenated anesthetic gases + nitrous oxide at the same time, the waste halogenated anesthetic gas REL is 0.5 ppm (NIOSH 2022). Sevoflurane is typically co-administered with nitrous oxide.

A select list of occupational exposure monitoring data is provided in Table 2. Studies published prior to 2015 were excluded as a timeline cut-off to ensure the table was not too long. In addition, studies that monitored exposure in the patient's breathing zone or that did area sampling in an inappropriate area (such as hallways) were excluded.

Table 2: Select Exposure Data to Sevoflurane

Location of Monitoring	Personnel Monitored / Details		Exposure [1]	Study
Surgery & PACU (post-anesthesia care unit)	Anesthesiologist	Induction	Mean 0.65 ppm ± 0.17 ppm	Herzog-Niescery et al 2015
		Repositioning	Mean 0.48 ppm ± 0.19 ppm	
		Extubation	Mean 0.59 ppm ± 0.35 ppm	
		PACU	Mean 0.74 ppm ± 0.35 ppm	
Surgery	Area	Operating Room 1	Mean 0.8 ppm (0.16-24.7 ppm)	Jankowska et al 2015
		Operating Room 2	Mean 3 ppm (0.18-60.9 ppm)	
		Operating Room 3	Mean 4 ppm (0.3-75 ppm)	
Surgery (pediatric)	Surgeon	Patient in laryngeal mask	Mean 1.05 ppm; Max 10.05 ppm	Herzog-Niescery et al 2016
		Cuffed tracheal tube	Mean 0.33 ppm; Max 1.44 ppm	
		Uncuffed tracheal tube	Mean 1.79 ppm; Max 18.02 ppm	
Surgery	Anesthesiologist		Mean 7.7 ± 8.7 ppm (0.2-34.4 ppm)	Souza et al 2016
Surgery	Anesthesiologist	Seated	Median 0.55 ppm	Sárkány et al 2016
		Standing	Median 0.37 ppm	
Surgery	Area		Geometric Mean 0.004 ± 1.56 ppm [2]	Jafari et al 2017
	Healthcare workers in operating room		Geometric Mean 0.005 ± 1.74 ppm [2]	
Surgery (pediatric)	Anesthesiologist	Patients with positive behaviours	Mean 4.38 ± 4.02 ppm Max 70.06 ± 61.08 ppm	Herzog-Niescery et al 2017
		Patients with negative behaviours	Mean 12.63 ± 8.66 ppm Max 252.86 ± 139.91 ppm	
Surgery [3] (after 120 minutes)	No waste gas scavenging	Anesthesia Area	20.0 ppm	Braz et al 2017
		Anesthesiologist	16.7 ppm	
		Nursing Assistant	16.1 ppm	
	Waste gas scavenging	Anesthesia Area	4.8 ppm	
		Anesthesiologist	3.3 ppm	
		Nursing Assistant	2.9 ppm	
PACU	Area	PACU 1	Median 0.12 ppm Max 0.96 ± 0.20 ppm	Heiderich et al 2018
		PACU 2	Median 0.11 ppm Max 0.82 ± 0.07 ppm	
PACU (pediatric)	Area	First week monitored	Mean 0.31 ± 0.20 ppm	Özelsel et al 2018
		Second week monitored	Mean 0.42 ± 0.40 ppm	
PACU	Area, middle of PACU		Mean 0.34 ± 0.07 ppm	Herzog-Niescery et al 2019
Pain management unit (applied topically)	Nurse (task-specific, 20-50 minutes / task)		Mean 5.86 ppm (2.86-9.12 ppm)	Fernández-Ginés et al 2019
	Nurse (longer-duration, all tasks)		8.48 ppm (3 hours + 25 minutes)	
Laboratory (operating room simulation)	Refilling a closed vapourizer filling system		Mean 0.10 ppm Max 0.16 ppm	Varughese and Bacher 2020

[1] When exposure is presented with ± after, it refers to ± 1 Standard Deviation. When exposure is presented with (number range in brackets) after, the range in the brackets refers to the exposure range.

[2] Study by Jafari et al (2017) identified a lognormal distribution. As a result, the authors indicate to use the geometric mean and geometric standard deviation, as oppose to the arithmetic mean and arithmetic standard deviation.

[3] Operating room in this study Brazil has 7 Air Changes per Hour (ACH), with 25% fresh external air and 75% recirculated air, which is 1.75 ACH fresh air (Braz et al 2017). This is lower than the standards adopted in other countries, including Canada and the USA. Currently, the US ranges from 15-20 ACH in building codes, but was formerly 12 ACH (Gormley and Wagner 2018) so many studies would have been done with 12 ACH. In practice, ventilation may be as high as 40 ACH (Gormley and Wagner 2018). Not all studies noted the ACH in the study, which makes it even more difficult to compare exposures in different studies with regards to ventilation. Further, PACU in majority of jurisdictions have same ventilation requirement as any patient care space, which is lower ventilation than operating rooms, typically 6 ACH (Gormley and Wagner 2018).

Adverse Health Effects

A narrative literature review by Herzog-Niescery et al (2018) concluded that exposure below 2 ppm sevoflurane (or isoflurane or desflurane) is not likely associated with organ dysfunction, neurotoxicity, or cognitive impairment. Their reasoning was not well elucidated. This research team has done occupational exposure monitoring for sevoflurane, with most mean exposures below 2 ppm (Herzog-Niescery et al 2015, Herzog-Niescery et al 2016, Herzog-Niescery et al 2019), with the exception of exposures when anesthetizing pediatric patients (Herzog-Niescery et al 2017). It is more difficult to fit masks and cuffs to pediatric patients, plus they are more likely to exhibit "negative" behaviours, described by the authors as thrashing or moving, often as a result of not understanding what is happening, being confused, or being upset. Other studies have drawn similar conclusions, that pediatric anesthesia results in higher exposures than adult anesthesia (Byhahn et al 2001). The review by Herzog-Niescery et al (2018) noted that there is a range of occupational exposure limits to sevoflurane in countries / jurisdictions, though they also noted that many counties simply do not have an occupational exposure limit.

Sevoflurane is three times more potent than desflurane (Eger 1993). However, potency does not translate to toxicity, and so would form only a crude estimation of risk when comparing occupational exposure limits.

The remainder of this section on adverse health effects will focus predominantly on primary research in humans.

Irritation

An investigational study in eleven healthy volunteers reported that sevoflurane produced irritation, though it produces less irritation than the halogenated anesthetic gases halothane, enflurane, and isoflurane (Doi and Ikeda 1993). The concentrations being given to elicit irritation were approaching concentrations used induce anesthesia, although the duration given was too short to induce anesthesia. It is difficult if not impossible to apply results of exposures at anesthetic doses to draw a conclusion regarding exposure at subanesthetic occupational exposures.

Hematopoietic / Cytotoxic / Genotoxic Effects

Some studies have noted immunological changes in those occupational exposed to anesthetic gases, particularly with regards to neutrophils and lymphocytes in humans (Casale et al 2014) and in animal models (Urner et al 2011). Casale et al (2014) note that the halogenated anesthetic gases reduce the expression of inflammatory mediators, which thus reduces proliferation of monocytes and neutrophils. Notably, Casale et al (2014) was looking predominantly at exposures to halogenated anesthetic gases other than sevoflurane, though they applied the results to sevoflurane based on animal models by Urner et al (2011).

A 2015 study compared 15 medical professionals exposed to anesthetic gases for 3 years to 15 healthcare workers not exposed to anesthetic gases (Chaoul et al 2015). The authors note that exposed healthcare workers were exposed to high levels of anesthetic gases, reported as: isoflurane > 7 ppm, or sevoflurane > 7 ppm, or nitrous oxide ≥ 100 ppm. There were no statistically significant differences in the concentrations of most pro-

inflammatory cytokines; however, the pro-inflammatory interleukin IL-8 significantly increased in those exposed to anesthetic gases.

The study by Hua et al (2021) involved participants with 2-25 years' service at a large hospital: 68 operating room healthcare workers regularly exposed to anesthetic gases, matched to 82 workers in the same hospital who were not exposed to anesthetic gases or other hazardous agents. Air monitoring was done on healthcare workers in the operating rooms, with a mean of 1.11 ± 0.65 ppm (range 0.07-3.84 ppm). Hua et al report that sevoflurane is the only anesthetic available in this region of China, reducing the effects from other anesthetic gases in most other occupational studies.

In the complete blood count (CBC) results, lymphocyte count and hemoglobin were both statistically significantly lower in the sevoflurane-exposed group than in controls, though only hemoglobin was lower than normal range. All other CBC parameters monitored were not statistically significantly different (red blood cell count, white blood cell count, blood platelet count, neutrophil count, eosinophil count, basophil count).

The study by Ji et al (2021) involved 28 anesthesiologists predominantly exposed to sevoflurane for at least 2 years, compared to residents who were not exposed to waste anesthetic gases. The mean exposure in the exposed group was 1.03 ppm (range 0.03-2.24 ppm). There was no significant difference in apoptosis rates, cell cycles, or subpopulations of lymphocytes between the groups.

Hemoglobin was found to be lower in one study when exposure was 1.11 ppm ± 0.65 ppm (range 0.07-3.84 ppm) (Hua et al 2021). Although this study also noted a statistically significant difference in lymphocytes, another study did not identify a statistically significant difference (Ji et al 2021).

Studies published by the same research group are similar in nature and allow for comparison (Souza et al 2016, Aun et al 2018, Braz et al 2020). The first study in chronological order was published by Souza et al (2016). This study concluded that chronic exposure to desflurane, isoflurane, sevoflurane, and nitrous oxide resulted in changes to DNA damage if exposure was 2 years or longer. In this study, 27 anesthesiologists with at least 2 years' exposure to waste anesthetic gases were matched to 30 physicians without exposure to anesthesia.

Typically, exposure was to one halogenated anesthetic gas at a time, without multiple exposures during the same case. Exposure was measured in the exposed group separately as follows:

Desflurane	16.4 ± 6.0 ppm (8.2 – 23.2 ppm)
Isoflurane	5.5 ± 4.4 ppm (0.4 – 16.5 ppm)
Sevoflurane	7.7 ± 8.7 ppm (0.2 – 34.4 ppm)
Nitrous oxide	150.3 ± 135.7 ppm (61.0 – 350.0 ppm)

Notes:

- Reported as Mean ± 1 Standard Deviation (Range in brackets)

This study has a noticeable limitation. The anesthesiologists were exposed to 4 anesthetic gases: nitrous oxide and the halogenated anesthetic gases of desflurane, isoflurane, and sevoflurane. Typically, it is expected that only one halogenated anesthetic gas (desflurane, isoflurane, sevoflurane) would be used per case, and thus exposure would

only occur to one halogenated anesthetic gas at a time. However, it is not possible to separate each anesthetic gas exposure to know if one anesthetic gas had more of an impact than the others.

Although the group monitored was small (n=27), a statistically significant change was identified when measuring genotoxic and cytotoxic effects. Specifically, a difference was noted in the anesthesiologists having higher frequency of genotoxic and cytotoxic effects through the buccal micronucleas cytome assay, karyorrhexis and pyknosis in lymphocytes by comet assay, and a lower frequency of basal cells, compared to the control group. The authors conclude exposure to halogenated anesthetic gases (desflurane, isoflurane, sevoflurane) and nitrous oxide results in genomic instability, cytotoxicity, and proliferative changes, detectable in those with at least 2 years' occupational exposure to anesthetic gases (Souza et al 2016).

Because both cases and controls were physicians with comparable levels of education and further matched for age, sex, and lifestyle; it is less likely that other confounding factors impacted these results. The main unknown is how much each anesthetic gas caused the health effects.

The second study cited by this group compared medical residents before and after exposure to anesthetic gases (Aun et al 2018). In this study, 26 medical residents in their first year of medical residency had biological monitoring done at the beginning of the program, six months after starting, and one year after starting. The residents were exposed to desflurane, isoflurane, sevoflurane, nitrous oxide. Typically, it is expected that only one halogenated anesthetic gas (desflurane, isoflurane, sevoflurane) would be used per case. The goal was to look for signs of DNA damage over the course of one year of exposure to waste anesthetic gases. No significant changes were identified in biomarkers of cytotoxicity or genotoxicity. The authors conclude brief occupational exposure of up to one year to anesthetic gases do not induce cytotoxicity or genotoxicity (Aun et al 2018).

The final study cited by this same group compared exposed medical residents to unexposed medical residents (Braz et al 2020). In this study, 32 surgical residents and anesthesiology residents were matched to 31 internal medicine residents. The assumption made was that surgical and anesthesiology residents would have higher waste anesthetic gas exposures, and the medical residents would not have waste anesthetic gas exposure. The authors do not clarify if they excluded medical residents who worked in ICUs, who may have exposure to waste anesthetic gases if patients are sedated. The survey was done at the end of 3 years of medical residency. The residents were exposed to isoflurane, sevoflurane, nitrous oxide. Typically, it is expected that only one halogenated anesthetic gas (isoflurane, sevoflurane) would be used per case, and thus exposure would only occur to one halogenated anesthetic gas at a time.

Typically exposure was to one halogenated anesthetic gas at a time, without multiple exposures during the same case. Exposure was measured separately as follows:

	No scavenging	Scavenging	Mean
Isoflurane	9.2 (3.0-17.8) ppm	1.3 (0.3-3.2) ppm	5.3 ppm
Sevoflurane	16.4 (5.3-34.1) ppm	2.9 (1.0-7.2) ppm	9.7 ppm
Nitrous oxide	235 (120-350) ppm	66 (61-70) ppm	180 ppm

Notes:

- Reported as Mean (Range in brackets)
- Surgical and anesthesiology residents worked in all operating rooms, in those with and those without waste scavenging systems

There was a statistically significant increase in basal DNA damage (Comet assay) in the exposed group, and a statistically significant increase in IL-17A. There was no statistically significant difference in genetic instability (micronucleus); oxidative stress markers (DNA, lipid and protein oxidation); antioxidant capacities; and most proinflammatory cytokine levels, with the exception of IL-17A (Braz et al 2020).

The next 3 studies are noted because they met the search parameters of this review, but were not well designed studies. A study investigating biomarkers of genotoxicity between anesthesiologist and controls identified a difference but it did not pass the test of statistical significance (Bozkurt et al 2002). The authors then explain the results by concluding all 14 of the female participants were in the same stages of their menstrual cycles, though menstrual status was not an intended goal of the study, and was not verified despite being easy to investigate. Next, a study comparing healthcare workers exposed to anesthetic gases to controls identified that the exposed group did not have differences in genotoxicity between the groups, but the exposed group was also statistically significantly more likely to smoke than the controls (Chandrasekhar et al 2006). The authors do not thoroughly address smoking as a confounder, which suggests the controls are not a good control group. Finally, a study comparing 100 healthcare workers exposed to anesthetic gases compared to 100 blood donors did not have adequate data on the control group (Szyfter et al 2016). Twenty-four out of 100 healthcare workers were smokers, but smoking status was not asked of the controls. In addition, the anesthetic gas exposure assessment was using data collected 12 years prior to the study, and the authors note that 2 years before the operating rooms were redesigned, making actual exposure unknown. The authors then conclude that the genotoxicity of anesthetic gases can be compensated by healthcare workers 3 factors: healthcare workers having efficient DNA repair; adaptive responses where exposed cells (*in vitro*) resist damage if there is prolonged exposure; and self-elimination of selective individuals to other jobs. These conclusions are not well substantiated, making this study unreliable.

In conclusion to this long section, the better designed studies identified cytotoxic, genotoxic, immunological effects in those exposed to sevoflurane and other anesthetic gases.

<u>Hepatic Effects</u>

Two studies were identified that investigated liver effects from occupational exposure to sevoflurane (Neghab et al 2020a, Hua et al 2021).

In the study by Neghab et al (2020a), 52 healthcare workers with at least 1 year exposure to waste anesthetic gases were matched to 52 administrative staff in the same hospital, with those with a history of renal or hepatic disease excluded. Exposure to waste anesthetic gases was measured in urinary concentrations. The healthcare workers had measurable urinary concentrations to nitrous oxide (175.8 ± 77.52 ppb), isoflurane (4.95 ± 3.43 ppb), and sevoflurane (15.03 ± 16.06 ppm). After adjusting for confounders, liver function tests were statistically significantly different between the healthcare workers and administrative staff in mean levels of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and alpha-glutathione-S-transferase; but not in other liver function parameters (serum albumin, total proteins, alkaline phosphatase, direct bilirubin, total bilirubin).

Neghab et al (2020a) hypothesize that waste anesthetic gas exposure may cause subtle, preclinical changes in liver function. That said, although the parameters are statistically significantly different, they are not clinically significant.

The study by Hua et al (2021) was described previously. Since sevoflurane is the only anesthetic available in this region of China, the results are not impacted by occupational exposure to other halogenated anesthetic gases. In the analysis of liver function: the total protein (can also measure kidney function) and total bilirubin were statistically significantly different between sevoflurane-exposed and control groups, though all results are in the normal range. The remaining parameters of liver function measured (total cholesterol, triglycerides, direct bilirubin, alanine aminotransferase, aspartate aminotransferase) were not statistically significantly different.

Although statistically significantly different results are noted in both studies, all results are still in the normal range in both studies. That said, it is possible that liver function could become impaired with continued occupational exposure. Notably, different parameters were statistically significantly different between the studies by Neghad et al (2020) and by Hua et al (2021), not pointing to any one factor consistently altered. No definitive conclusions can be drawn from these studies' results.

Renal Effects

In the literature review, three studies were identified that investigated renal effects in humans with occupational exposures to sevoflurane: a study by Trevisan et al (2003), a study previously described by Neghab et al (2020a), and a study previously described by Hua et al (2021).

In the study by Trevisan et al (2003) a total of 61 healthcare workers were monitored for occupational exposure to sevoflurane and nitrous oxide, with select renal effects compared to controls, which were healthcare workers without anesthetic gas exposure. Renal effects monitored in both groups included total urinary proteins excretion, N-acetyl-b-D-glucosaminidase, and glutamine synthestase. Among the exposed healthcare workers: when exposed to an open circuit, mean exposure was 34.9 ppm (0.87-99.45 ppm) nitrous oxide and 0.41 ppm (0.02-1.88 ppm) sevoflurane; when exposed to a semi-closed circuit, mean exposure was 28.3 ppm (0.88-111.61 ppm) nitrous oxide and 0.18 ppm (0-1.4 ppm) sevoflurane.

Total urinary proteins, N-acetyl-b-D-glucosaminidase, and glutamine synthestase results were all within normal ranges for both the waste anesthetic gas exposed group and the controls. There was no statistically significant difference between exposed and control groups with regards to N-acetyl-b-D-glucosaminidase or glutamine synthestase. There was a small and statistically significant difference between the exposed and control group for total urinary proteins, though there was no dose-response relationship between sevoflurane and total urinary proteins. A dose-response relationship was observed between sevoflurane exposure and both N-acetyl-b-D-glucosaminidase and glutamine synthestase, but not statistically significant. All results were in normal ranges. The authors conclude that the occupational exposure levels in this study do not have a clinical effect on kidney function, though higher exposures may (Trevisan et al 2003). However, the results are in normal ranges, making it difficult to draw definitive conclusions.

The study by Neghab et al (2020a) was described previously. Since sevoflurane is the only anesthetic available in this region of China, the results are not impacted by other anesthetic gases. After adjusting for confounders, kidney function tests were statistically significantly different between the healthcare workers exposed to sevoflurane and administrative staff in mean levels of serum creatinine, kidney injury molecule-1, and calcium; but not in other kidney function parameters (blood urea nitrogen, potassium, phospohorous). As with liver function, the authors hypothesize continued waste anesthetic gas exposure may cause subtle, preclinical, and prepathological changes in kidney function, but that more study is required.

The study by Hua et al (2021) is briefly described in the previous section. As noted, occupational exposure to sevoflurane was a mean of 1.11 ± 0.65 ppm (range 0.07-3.84 ppm), and it was the only anesthetic gas in use. In the analysis of kidney function: the total protein (can also measure liver function) and creatinine were statistically significant in difference between exposed and control groups. The remaining parameters of kidney function measured (blood urea nitrogen, uric acid) were not statistically significantly different. Although the authors do not comment on if the results are clinically different, it is noted in this review that all results are in normal ranges.

The studies by Trevisan et al (2003), Neghad et al (2020a), and Hua et al (2021) result in statistically significant results in some kidney function parameters, but not the same parameters in each study. It is noted that despite statistically significantly different results, all results were within normal ranges. It is possible that kidney function could become impaired with continued occupational exposure, but unknown. No conclusions can be drawn from these results.

Teratogenic Effects

A 2001 review noted that there is no evidence of teratogenicity from occupational exposure in the first trimester (Byhahn et al 2001). However, the authors only cite one case report relating to sevoflurane exposure. A 2019 review noted there is some evidence that sevoflurane may result in neurodevelopment effects if used as for anesthesia in the second trimester of pregnancy (Chai et al 2019). This review's conclusion is based on studies in which it is an anesthesia administered in pregnancy, which requires short-term exposure many times higher than occupational exposures. Many animal models were also identified in this review (uncited), although results were mixed.

Conclusions

Most exposed healthcare workers were exposed to multiple halogenated anesthetic gases (though only one at a time) + nitrous oxide, making it difficult to ascribe a result conclusively to one exposure. There are only a small number of studies out of regions of China where the exposed group was only exposed to sevoflurane.

It is recommended that an ACGIH® TLV®-TWA be introduced at 0.2 ppm. This is based on the study by Souza et al (2016), in which exposure to sevoflurane of a mean of 7.7 ± 8.7 ppm, range 0.2 – 34.4 ppm resulted in evidence of genotoxic and cytotoxic effects in anesthesiologists with at least 2 years' exposure. This value would be a protective, evidence-based occupational exposure limit.

Citable Material

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