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

Eastern Region - Ottawa Clinic
1545 Carling Avenue, Suite 110
Ottawa, ON K1Z 8P9
Tel: (613) 725-6999
Fax: (613) 725-1719
ottawa@ohcow.on.ca
www.ohcow.on.ca

March 31, 2023

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® and BEI® 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, Stoddard solvent, and Welding Fumes. The submissions for Diesel Exhaust, Nickel and nickel compounds, and Welding Fumes are updates from our 2022 submissions. Lead is a BEI® only, updating our 2022 submission.

Thank you for the opportunity on behalf of our team.

Sincerely,

Krista Thompson, MHSc, ROH, CRSP
Occupational Hygienist, OHCOW
kthompson@ohcow.on.ca

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Date Submitted March 31, 2023

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

Name of Group/Individual Submitting Comments Occupational Health Clinics for Ontario Workers Inc. (OHCOW)
Authored by: Kevin Hedges, PhD, MAppSc, BSc, DipEd, COH, CIH
Reviewed by: Krista Thompson, MHSc, ROH, CRSP Occupational Hygienist, Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP Executive Director

Contact Information

Address 1090 Don Mills Road, Suite 606
Toronto, ON M3C 3R6
Canada

Telephone: 416-510-8713 Email: Koconnell@ohcow.on.ca

Executive Summary *(limit 250 words)*

There is now definitive evidence from more recent studies since the ACGIH 2007 feasibility assessment. Research carried out on the McIntyre project and others linking exposure to aluminum and aluminum compounds with neurological orders merits a review by the ACGIH and assigning a BEI®.

Literature for McIntyre Powder-related publications have demonstrated that inhaled aluminum can translocate into the bones and quantified by neutron activation analysis. The method provided by Bickley 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: Krista Thompson (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*): see below

Specific Action Requested

1. We recommend a BEI® for Al in urine of 50 µg/g creatinine, based on the work of Klotz and Hartwig (2020) and the cited McIntyre powder research.
2. We recommend the TLV®-TWA be lowered.

Rationale

Genetic, neuropathological, and biochemical investigations have revealed meaningful relationships between aluminum (Al) exposure and neurotoxic and hematotoxic damage (Turkez et al. 2022).

Occupational exposure to aluminum occurs mainly via inhalation of fumes containing aluminum and aluminum compounds, such as during welding processes. Inhaled aluminum can accumulate in the bones, which has a relatively long half-life of 10-20 years. A similar half-life is noted for accumulation in the brain. Lung and bone burdens explain the long serum and urine half-lives which may be more than one year such as for welders after cessation of exposure. This is why setting a BEI® is important: it should drive exposure reduction and thus prevent accumulation and any further increase in body burden.

The main target organs are the central nervous system and lungs. Various in vivo and in vitro studies show that aluminum can influence more than 200 biologically important reactions in the nervous system (Klotz et al. 2019). Inhalation of aluminum can also cause aluminosis. Other toxic effects (e.g. on **bones** and **blood**) as well **developmental toxicity** are described in the MAK Value Documentation. In humans, aluminum has been reported to have pathogenic effects on the lungs. Aluminosis occurs at aluminum concentrations of more than 200 µg/L urine.

Firstly, even though this submission addresses a proposed BEI® for aluminum, we should highlight that the current TLV®-TWA for aluminum metal and insoluble compounds of 1 mg/m^3 (respirable) is set too high. There may be many situations where a significant portion of respirable particulate matter is sub-micron (< 1 µm) or even ultrafine (< 0.1 µm), necessitating a lower TLV®-TWA.

It is now known that ultrafine airborne aluminum particulate matter can enter and be deposited in the brain. Aluminum could enter the brain from systemic circulation or the site of absorption.

Aluminum fluxes into brain across the blood-brain barrier (BBB), the choroid plexuses and the nasal cavity. Al is considered unsafe to humans after the discovery of increased levels of Al in brain tissues of patients with encephalopathy, having been exposed to Al accumulation through dialysis (Igbokwe et al. 2019).

Redistribution of aluminum out of the brain is slow. Aluminum can be deposited in the brain for a long time (Wang 2018). Aluminum entering the brain across the blood-brain barrier has been defined to be the primary route of brain aluminum uptake. A recent study to examine 100 of the most cited articles on the toxicology of aluminum related to the current state of knowledge has been provided by de Lima et al. 2022.

Publications between 1945 and 2022 found Alzheimer's disease (AD). Aluminum and neurotoxicity were found as the most frequent keywords. The articles most cited in world literature suggested that aluminum exposure may be associated with Alzheimer's disease, Parkinson's disease (PD) and parkinsonism, dialysis

encephalopathy, amyotrophic lateral sclerosis (ALS), neurodegeneration changes, cognitive impairment, bone damage, oxidative alterations, and cytotoxicity.

As noted, based on the above we recommend that the ACGIH places aluminum on the under-study list in order to establish a much lower TLV®-TWA based on the most up to date evidence. Especially as the current TLV® documentation (2007) is outdated.

Martin et al. (2022) notes that serum aluminum is the main biomarker of toxicity. For cases of continuous exposure, urine testing is recommended. The solubility of aluminum compounds determines its toxicokinetic health risks. For miners forced to inhale McIntyre power, aluminum hydroxide dominates the aluminum speciation (Zarnke et al. 2019). Although aluminum hydroxide is insoluble in water, the PH in the gastrointestinal tract will increase the bioavailability of aluminum. In addition, it needs to be considered that the particle size and the surface area influences the bioavailability of substances of low solubility (ECHA nd.).

A study of smelter workers revealed that 22 and 95 µg/g of urinary Al was associated with exposure to 1 mg/m³ total Al and 1 mg/m³ soluble Al, respectively.

Increases in the levels of Al in the urine of workers show that exposure by inhalation does lead to transfer to the systemic circulation, most likely with a significant contribution from uptake in the gastrointestinal tract following "mucociliary clearance" (ECHA nd.).

Urine is the measurement of choice as it has a higher sensitivity. In workers exposed to aluminum, urine concentrations 1 or 2 days after exposure is a reliable indicator of aluminum concentrations in the body.

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 papers that can be used to guide the establishment of a BEI® 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 aluminum detected in the lungs from autopsies of former miners, and aluminum in bone detected in retired miners some 40 years after exposure and health effects including neurodegenerative disease provides useful study source material.

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 strong likelihood for translocation of aluminum particles into brain tissue.

Regarding aluminum in bone, the Bickley et al. 2022 study was able to demonstrate that aluminum can be measured in the bones of retired miners exposed to McIntyre Powder who had been exposed over 40 years ago using neutron activation analysis. 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.

A recent cohort study by Demers et al. 2020, investigated the association of McIntyre powder 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 in Ontario, 28% of all underground miners were exposed, with the peak being in 1961.

Of these exposed miners, 90% were exposed after 1956. When looking at the rate of PD and parkinsonism, there was a 27% and 14% increase in incidence rates of PD and parkinsonism compared to the general population.

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 (10-20 years) (Priest 2004) 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 as described, miners inhaled aluminum nanoparticles mostly in the form of aluminum hydroxide, are useful when trying to understand both the bioavailability and body burden of aluminum.

Further analysis of this data set by Priest (2004), 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 using formulae by Laureys and Hoet 2001.

The German Federal Environmental Agency (Umweltbundesamt) established provisional reference values for the general population using concentrations of aluminum in both urine and serum, which amount to <15 µg/L and <5 µg/L, respectively (Klotz et al., 2017).

Poddagolda et al. 2021, reported that for oral exposure to aluminum, 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), which provides a useful reference.

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 aluminum, 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 aluminum is presented; this value is oriented towards the 95th percentile (DFG 2019). This value is 50 µg aluminum/g creatinine (µg/l: 1.2 µg Al/l = 1 µg Al/g creatinine).

In 2017, a BAT value for aluminum 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.

By definition, BAT values can be established only for such substances that 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 humans. 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.

Aluminum in urine as a biomarker for pre-clinical neurological effects

Epidemiological studies have been conducted to investigate neurotoxic effects by identifying the two major functional areas involved in motor and cognitive functions using different test methods (Klotz et al. 2019). Klotz et al. 2019 notes that the most sensitive endpoint for the derivation of a health-based BAT value for aluminum is the occurrence of preclinical neurotoxic effects after exposure. Studies indicate that there is an association between aluminum in urine or serum and central nervous system effects. The direct correlation between CNS and aluminum in urine has been used as a basis for deriving a limit of urinary aluminum of 3 nmol/L, 2.3 µmol/g creatinine, or 62 µg/g creatinine. An updated German BAT value is in fact based on a direct correlation between the correlation of subclinical neurological effects in aluminum exposed workers and urinary aluminum levels. We believe this is a better approach to assign a BEI® value than applying a correlation based on personal exposure that is seemingly too high. The updated BAT value is 50 µg/g creatinine with a sampling time after several shifts or at the end of the work week.

Refer to Figure 1 (next page).

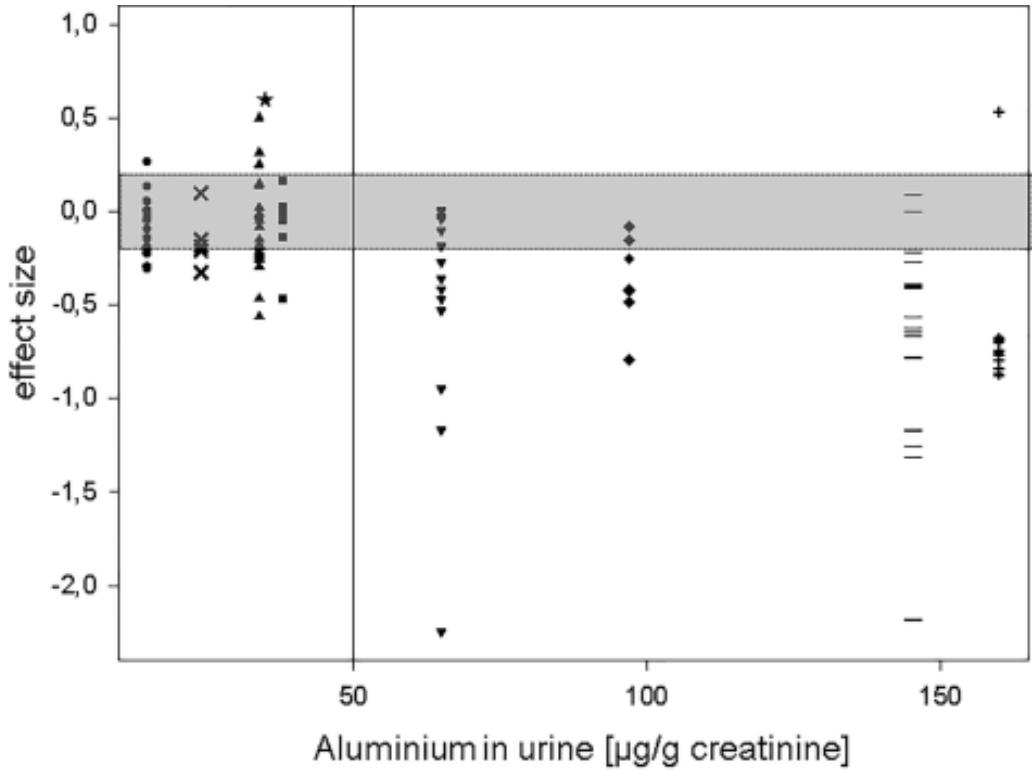

Figure 1. Adapted from Klotz et al. (2019), the above figure combines information from nine studies showing cognitive effect sizes relative to the median of urinary aluminum concentrations. An effect size below zero demonstrates an adverse motor or cognitive effect. The studies show a trend between poorer cognitive performance with increasing urine aluminum concentrations. According to Klotz et al. 2019, "cognitive effects > 50 µg/g creatinine go beyond the measure of "negligible effect".

This level is also below the tolerable weekly intake (TWI) from derivation of Biomonitoring Equivalents for aluminum for the interpretation of population-level biomonitoring data reported by Poddalgoda et al. 2021, at a level of 57 µg / g creatinine.

The literature indicates that urine aluminum concentrations below 55 µg/g of creatinine are safe for humans. While the level of urinary aluminum 4 to 6 µmol/L (108 to 162 µg/L) represents a threshold for neurological side effects, urine level of 100 µg per liter is known as the critical concentration and the development of neurological complications (Amiri et al. 2022).

Aluminum reduces the activity of acetylcholinesterase. In addition, exposure to aluminum significantly reduces the activity of gamma-aminolevulinic acid dehydratase (ALAD) in blood and gamma-aminolevulinic acid synthesis (ALAS) in brain (Amiri et al. 2022) – this warrants further investigation and paves the way for future research on biological monitoring of effects.

Conclusions

We recommend consideration proposing a BEI® for Al in urine of 50 µg/g creatinine based on the work of Klotz and Hartwig (2020) and the McIntyre powder research.

Citable Materials

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Date Submitted March 31, 2023

Chemical Substance **Diesel Exhaust**
(8 pages + citable materials)

Name of Group/Individual Submitting Comments Occupational Health Clinics for Ontario Workers Inc. (OHCOW)
Authored by: Kevin Hedges, PhD, MAppSc, BSc, DipEd, COH, CIH
Reviewed by: Krista Thompson, MHSc, ROH, CRSP Occupational Hygienist; Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP Executive Director

Contact Information

Address 1090 Don Mills Road, Suite 606
Toronto, ON M3C 3R6
Canada

Telephone: 416-510-8713 Email: Koconnell@ohcow.on.ca

Executive Summary *(limit 250 words)*

Elemental carbon (EC) is used as an indicator for diesel exhaust by most jurisdictions. The European Union has decided on an occupational exposure limit of 0.05 mg/m^3 EC, in effect from 2023, which is the same limit in Germany and Sweden. The Australian Institute of Occupational Hygiene recommends a limit of 0.1 mg/m^3 EC, though Cherrie 2019 noted that a limit of 0.1 mg/m^3 "would do little to reduce the predicted death toll from occupational exposure to diesel exhaust particulate."

Long et al (2022) studied controlled human exposure to diesel exhaust from traffic air pollution and reported findings including a controlled human experiment which included 40 volunteers, who had an acute exposure of PM2.5 at 25 µg/m^3 (0.025 mg/m^3). At this level, adverse effects on endothelial function, vascular walls, and heart rate variability even at 24 h post-exposure were reported. In addition, the study by Chen et al (2017), between 2001 and 2012, in Ontario, Canada, found an adjusted incident dementia hazard ratio (HR) of 1.07 for people living less than 50 m from a major traffic road (95% CI 1.06–1.08).

Based on shorter term acute exposures, we recommend a TLV®-TWA for EC of 10 µg/m^3 EC with (L) notation as an evidence-based limit for all workplaces.

As diesel exhaust is in the "under study" list, we provide the following recommendation: a TLV®-TWA of 60 pg/m^3 for 1-nitropyrene (1-NP) especially where EC is at relatively low levels of exposure / approaching the limit of quantitation using NIOSH 5040.

Chemical Substance: Diesel Exhaust

Contact Name: Krista Thompson (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*): see below

Specific Action Requested

1. We recommend 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. We recommend 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) note an increase at about ~ 6 pg/m^3 for 1-NP per 1 µg/m^3 increase in EC which equates to 60 pg/m^3 of 1-NP in total corresponding to a proposed ACGIH TLV®-TWA of 10 µg/m^3 EC.

Rationale

1.0 Introduction

Chronic inhalation studies on rats with diesel exhaust from "new diesel engine technology" (Mauderly 2010; HEI, 2015b) with the highest concentration of approximately 10 µg/m^3 diesel soot particles, provided no evidence of pulmonary carcinogenicity. For older engines, Ge et al (2020) has reaffirmed findings from previous meta-analysis. Excess Lifetime Risks (ELR) associated with 45 years of EC exposure at 50, 20, and 1 µg/m^3 were 3.0%, 0.99%, and 0.04%.

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). 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 (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, has been derived. For the chronic particle-related inflammatory effect endpoint, Mauderly et al (1987), derived an OEL of 50 µg EC/m³ for rats.

As the soot core is believed to be the cause of the chronic effect of diesel engine emissions; the derivation is based on the EC. It should be noted that this assessment is based on "chronic effects" rather than "acute effects". The AGS 2017 derived particle-related inflammatory effects are based on chronic exposure. Acute exposures are not used to derive the limit value.

We believe that the ACGIH TLV®-TWA should be based on short term (acute) health effects. Chronic health effects will be compounded from acute health effects. Chronic inhalation studies in rats, derived an acceptance risk of 4:100,000 from a Human Equivalent Concentration (HEC) of 24 µg/m^3 (AGS 2017).

For shorter term exposure resulting in health effects, a study by Anderson et al (2019) reported adverse 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 this study 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) was 10.3 µg/ m^3 over 3 days of exposure.

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

2.0 Measures for exposure assessment

2.1 Ultrafine particles

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). Regarding women of reproductive capacity, Lavigne et al 2020 (p. 15) evaluated a total of 1,066 childhood cancers and found that first trimester exposure to UFPs of 10,000/cm^3 resulted in a Hazard Ratio (HR) of 1.13, 95% CI: 1.03–1.22. In the last five years, substantial progress has been made to assess personal exposure to ultrafine particles. Particle number concentration is dominated by the smallest particles (<200 nm), those which contribute nearly negligibly to particle mass concentration (Koehler and Peters, 2015). As diesel particulate matter (DPM) is predominantly < 1µm in diameter then measuring particle number may be a better surrogate for exposure and health effects compared to EC (NIOSH 5040) which is mass based.

2.2 Elemental carbon

For a mass-based measure, 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".

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). 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 a working range of approximately 6 to 630 µg/m^3, with an LOQ of ~ 2 µg/m3 for a 960-L air sample.

This requirement is described in ISO 15202- 35, while 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/m^3 NIOSH (2016), limits the TLV®-TWA to no less than 20 µg/m^3, the same level proposed by the ACGIH in 2001.

Verpaele (2018) 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.

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).

2.3 1-nitropyrene (1-NP)

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 study by Riley et al (2018), to evaluate of 1-NP as a surrogate measure for diesel exhaust found high correlations between the quantiles of 1-NP and EC exposures. 1-NP may in fact be a better surrogate, especially when assessing personal exposure < 20 µg/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 also 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/m^3 would equate to ~ 60 pg/m^3 1-NP. In addition, to further understand what an appropriate limit for 1-NP would be, figure 1.1 in IARC 2018 (monograph 105) can be used for comparison.

3.0 Levels of exposure

3.1 Levels of EC exposure in the most highly exposed industry – mining

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.

A 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. 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 overall diesel exhaust exposure. A recent study of Swedish exposures monitored in 2019 found that underground miners had an average geometric mean (GM) EC exposure concentration of 7 µg/m^3 with a geometric standard deviation (GSD) of 2.7 (Cren et al 2022).

3.2 Levels of exposure other workplaces

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 of 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) may exceed 0.01 mg/m^3.

4.0 Health effects

4.1 Cancer

The SHEcan project predicted that around 230 000 people will die from lung cancer from workplace exposure to diesel exhaust particulate in the EU (Cherrie 2019).

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).

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 0.03 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.

A reanalysis of a German Potash Miners cohort, by Möhner et al 2013, supports 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. 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 about 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 impetus for continuous improvement and target those workplaces with greatest risk.

Taxwell and Santonen (2016) note that 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). As noted, setting a health based TLV® for cancer is currently not feasible, if feasibility is to be considered. Therefore, 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".

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 approximate to 0.075mg/m^3 EC, although this is questionable and may not apply to all diesel engines. This is empirical, and the ratio will not be constant with a wide variation. Nasal, throat and eye irritation are 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/m^3 (≈ 75 to 225 µg EC/m^3).

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 /m3 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.

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, reaffirmed 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) suggests 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 health-based calculated occupational cancer risk values (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 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 particulate matter (DPM) to protect against adverse effects on the respiratory system.

4.2 Health effects from chronic exposure for non-cancer health effects

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). This is based on the endpoint of chronic particle-induced inflammatory action, the study by Mauderly et al (1987) derived from rats an AGW of 50 µg EC/m^3. The AGS didn't incorporate short term exposure in their assessment.

4.3 Health effects from short-term exposure for non-cancer health effects

For lung inflammatory changes diesel exhaust particles have been assessed using 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.

Taxwell and Santonen (2017) from human inhalation studies (1–2 h) have reported inflammatory changes in BAL/BW, and increased airway resistance at the lowest observable adverse effect level of 0.1 mg/m^3 of diesel exhaust particulate (DEP) (DECOS 2019) equivalent to about 0.05 mg/m^3 EC assuming a 50% conversion.

A study by Anderson et al (2019) demonstrated health effects for 29 healthy volunteers 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) 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. 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; suggesting that if a TLV®-TWA were assigned as 10 µg/m^3 an impetus for continuous improvement would drive further reductions.

4.4 Health effects and a dose response relationship from traffic pollution (ambient air studies)

Exposure to traffic pollution has been found to increase the incidence of several cardiopulmonary diseases, as well as type II diabetes, and is related to neurotoxicity as well as cancers (HEI 2013).

The most prominent effects caused by air pollution in both humans and animals are oxidative stress and neuro-inflammation. Studies in mice acutely exposed to DE (250-300 µg/m^3 for six hours) have shown microglia activation, increased lipid peroxidation, and neuro-inflammation in various brain regions, particularly the hippocampus and the olfactory bulb (Costa et al 2017).

In a recent human study (Gawryluk et al 2023) it was shown that brief diesel exhaust exposure of 120 minutes acutely impairs functional brain connectivity at a nominal concentration of 300 µg of particulate matter of 2.5 microns or less ($PM_{2.5}$)/m^3. During exposure, participants cycled on a stationary bicycle at light effort (that which yields ventilation at 15 L/min/m^2) for 15 min, during the first quarter of each hour, to maintain a representative level of activity.

An extensive review of the literature by Long and Carlsten (2022) included 104 publications of controlled human exposure studies to diesel exhaust along with traffic pollution. Health effects noted included cardiovascular system (e.g., vasomotor dysfunction, inhibition of fibrinolysis, and impaired cardiac function) and respiratory system (e.g., airway inflammation, increased airway responsiveness, and clinical symptoms of asthma). From this review the lowest exposure examined, a nominal concentration of diesel exhaust PM2.5 at 25 µg/m^3, resulted in acute diesel exhaust exposure associated with adverse effects on endothelial function, vascular walls, and heart rate variability even at 24 h post-exposure. Short-term exposure to diesel exhaust fumes has a prolonged adverse impact on endothelial function and vascular wall properties, along with impaired heart rate variability, abnormal fibrinolytic activity and increased markers of inflammation. An increased cardiovascular risk has been shown for 40 healthy subjects in a controlled human exposure experiment, when exposed to diesel exhaust fumes at an average exposure to PM2.5 at a concentration of 25 µg/m^3 (Tousoulis et al 2020).

DE was also associated with increased inflammatory markers and abnormal fibrinolytic markers. A study conducted in the US reported that a 10 µg/m^3 increase in PM2.5 increased cardiovascular mortality risk by 8–18% (Long et al 2022A).

Therefore, this justifies setting an ACGIH TLV®-TWA of no more than 10 µg/m^3 measured as EC based on the lowest observable adverse effects level (LOAEL) from short term health effects from both controlled human and traffic related exposure studies.

5.0 Conclusion

The review by Long et al 2022, demonstrated that diesel exhaust (PM2.5) at 25 µg/m^3 from acute diesel exhaust exposure in a controlled exposure experiment with 40 healthy individuals was associated with adverse effects on endothelial function, vascular walls, and heart rate variability even at 24 h post-exposure.

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, 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 reduce health impacts of non-cancer 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 as 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.

Recognizing that the ACGIH does not consider feasibility, it is nonetheless noted that providing a TLV®-TWA for diesel exhaust, measured as Elemental Carbon (EC), of 10 µg EC mg/m^3 is in fact 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.

6.0 Citable Material

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Date Submitted March 31, 2023

Chemical Substance **Lead BEI®**
(5 pages + citable materials)

Name of Group/Individual Submitting Comments Occupational Health Clinics for Ontario Workers Inc. (OHCOW)
Authored by: Shirly Yan, MPH, CIH, CRSP; Khayati Patel, MPH Occupational Hygienists
Reviewed by: Krista Thompson, MHSc, ROH, CRSP Occupational Hygienist; Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP Executive Director

Contact Information

Address 1090 Don Mills Road, Suite 606
Toronto, ON M3C 3R6
Canada

Telephone: 416-510-8713 Email: Koconnell@ohcow.on.ca

Executive Summary *(limit 250 words)*

Lead is one of the most vital occupational and environmental pollutants and has been linked to health problems, including cardiovascular disease, reproductive issues, central nervous system, renal, hematological damage, and carcinogenic effects. The biological exposure index (BEI) for lead exposure adopted by the ACGIH is <30 ug/dL and is mainly determined by measuring blood lead levels (BLL), as an indicator of the body burden of lead exposure in workers. However, studies suggest that lead exposure can cause health effects even at levels below the BEI® (Lee et al., 2022).

Numerous studies have found an association between low BLL (<5 ug/dL) and cardiovascular health, renal dysfunction, genotoxicity, and the hematological system. Lead is not only inhaled upon exposure, but uptake can occur by ingestion (often through cross-contamination during work processes) and some skin absorption. Julander et al. 2020 found that ingestion yielded the highest contribution. According to the Centers for Disease Control and Prevention (CDC), all exposure to lead can induce pathology, with BLL > 5 ug/dL the threshold considered to be elevated in both children and adult; therefore, this submission is recommending a BLL of <5 ug/dL (CDC, 2021). The Australian Institute of Occupational Hygienist (AIOH) suggested reduction of BLL to be less than 5 ug/dL for females of reproductive capacity. Several health institutions stated BLL of 5 ug/dL and greater is considered elevated and requires clinical action.

Occupational Health Clinics for Ontario Workers (OHCOW) recommends that the ACGIH® BEI® be lowered to 5 ug/dL (50 ug/L) to ensure workers are adequately protected.

Chemical Substance: Lead BEI®

Contact Name: Krista Thompson (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*): see below

Specific Action Requested

1. We recommend the ACGIH® BEI® be lowered to 5 µg/dL to ensure protection from both the carcinogenic effects, renal, hematological effects and the most sensitive toxic effects, namely damage to the nervous system.

Rationale

1. *Review of Other Guidelines*

According to California Department of Public Health, the mean blood lead level (BLL) for US adults is less than 1 ug/dL, and the 97.5 percentile for BLL is 3.5 ug/dL (CDPH, 2021); thus, CDPH recommends clinical action and follow up for adult BLLs 3.5 ug/dL and greater for the care of adults aged 18 and older and adolescents exposed to lead at work. Furthermore, Mount Sinai hospital, in New York indicates that in adults, the BLL of 5 ug/dL is considered elevated (Mount Sinai, 2021).

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 5 ug/dL. (AIOH Exposure Standards Committee, 2018).

2. *Literature and Documents for Low Level Lead Exposure*

Lead is mainly absorbed through the respiratory and digestive systems with some skin absorption. Exposure to lead has been linked to several disorders, including respiratory, neurological, cardiovascular, and urinary, which are associated with inflammatory, immune-modulation, and oxidative mechanisms. Lead can disturb the inflammatory system and result in increased inflammatory mediators in human, experimental animal, and cell culture systems. The mechanisms are well investigated. 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 dysregulation 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).

<u>The Association</u> <u>between Low Level Lead Exposure and Cardiovascular Health</u>

(Lanphear et al., 2018), a population-based cohort study of 14,289 adults with geometric mean concentration of blood lead level of 2.71 ug/dL (geometric SE 1.31). During median follow up of 19.3 years, 4422 people died, 38% from cardiovascular disease and 22% from ischaemic heart disease. An increase in the concentration of lead in blood from 1.0 ug/dL to 6.7 ug/dL, which represents the tenth to 90^{th} percentiles, was associated with all-

cause mortality (hazard ratio 1.37, 95% CI 1.17-1.60), cardiovascular disease mortality (HR 1.70, 95% CI 1.30-2.22), and ischaemic heart disease mortality (HR 2.08, 95% CI 1.52-2.85). In analysis restricted to participants who had concentrations of lead in blood lower than 5ug/dL, an increase in lead in blood from 1.0 ug/dL to 5.0ug/dL, which represents the tenth to 80th percentiles, was associated significantly with all-cause mortality (HR 1.38, 95% CI 1.15-1.66), cardiovascular disease mortality (HR 1.95, 95% CI 1.46-2.60), and ischaemic heart disease mortality (HR 2.57, 95% CI 1.56-4.52). Therefore, this study shows that concentration of lead in blood lower than 5ug/dL are associated with all-cause mortality, cardiovascular disease mortality, and ischemic heart disease mortality. Concentration of lead in blood lower than 5 ug/dL were associated with an increased risk of cardiovascular disease mortality. They also found risk coefficients for cardiovascular disease in the subset of participants with concentrations of lead in blood lower than 5 ug/dL were generally larger than coefficient in the total sample. Indicating the rate of increase in mortality was greatest with low amount of lead in blood.

Cardiovascular-related clinical markers were elevated in this cross-sectional study of United States adults (aged 20 and older) exposed to lead through the National Health and Nutrition Examination Survey 2007-2008 and the 2009-2010 datasets. In four quartiles of exposure – 0-2 ug/dL, 2-5 ug/dL 5-10 ug/dL, and 10 ug/dL and over, clinical and anthropometric markers were evaluated to examine how the markers manifested in the quartiles. 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 ug/dL and individuals with higher BLL of 2-5 ug/dL; and even more difference were found with higher BLL of 5-10 ug/dL. This indicates a potential relationship between higher lead exposure and increasing systolic blood pressure (Obeng-Gyasi et al., 2018). The authors further investigate the association between low BLL and increased oxidative stress in a 2020 pilot study, where they consider allostatic load, a measure of chronic stress and cardiovascular disease. They found a positive association between BLL of 3 ug/dL and increased oxidative stress and inflammatory responses (Obeng-Gyasi & Obeng-Gyasi, 2020).

A recent study was conducted to investigate the association between BLL and hypertension in adults when lead exposure for the general population is low by utilizing data from the US National Health and Nutrition Examination Survey (NHANES) 1999-2016. The study found a positive association between low BLL (MEAN=2.20 ug/dL) and higher diastolic blood pressure (Teye et al., 2020). Significant association between BLL and hypertension was also observed in a study investigating the health effects of lead exposure among communication radio-repair workers in a plant building in Thailand. (Thongsringklee et al. 2021).

<u>The Association between Low Level Lead Exposure and Renal Dysfunction</u>

A case study of paint workers with normal blood pressure and blood lead level as low as 4 ug/dL were found to have elevated risk of renal dysfunction (odds ratio (OR) 2.784, 95% CI 1.475-5.25) (Wang et al., 2018). Low lead exposure leading to renal dysfunction is further demonstrated in a case-cohort study investigating the impact of chronic lead exposure on liver and kidney function and hematologic parameters, in this study they found that there was a significant relationship between BLL and white blood cell and serum urea, hepatic transaminases, and creatinine (Nakhaee et al., 2019).

The Association between Low Level Lead Exposure and Genotoxicity

A study was conducted to investigate whether low lead exposure (<10 ug/dL) affects the sperm quality and the results indicated that aberrant DNA methylation of the calcium homeostasis pathway, induced by low lead exposure is a potential case for reduced sperm velocity (Zhang et al., 2021).

The Association between Low Level Lead Exposure and Hematological System

A key enzyme for the synthesis of heme is δ- aminolevulinic acid dehydratase (ALAD). δ-ALAD, a cytoplasmic enzyme rich in SH groups, is the enzyme that catalyzes the formation of porphobilinogen from -aminolevulinic acid (ALA). In one of the studies, it was demonstrated that δ-ALAD is inhibited when lead BLL are as low as 5 ug/dL and leads to behavioral changes and childhood lead encephalopathy (Collin et al., 2022). The inhibition of δ-ALAD results in the accumulation of δ-ALA in the plasma and excess of δ-ALA leads to severe neurological effects (Dehari-Zeka et al., 2020). Moreover, a cross-sectional study among male steelworkers was conducted to examine the relationship between serum γ-glutamyl transpeptidase (γGT) as a human index of oxidative stress and BLLs less than 5 ug/dL, a cause of oxidative stress. The study concluded that BLL was positively associated with serum γGT levels in male steelworkers even at low lead concentrations (<5ug/dL) (Lee et al., 2022).

Animal Studies

Animal studies on adult mice were conducted and it was found that exposure to the lowest (30 ppm lead acetate, mean BLL 3.4 ug/dL) and highest (330 ppm lead acetate, mean BLL 14.1 ug/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. Due to this, 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).

3. *Review of Multiple Routes of Exposure and Mechanism*

As mentioned above, lead is absorbed predominately from the respiratory and digestive systems, though skin absorption can occur. The effect of multiple routes of lead exposure to body burden was investigated in a case study by Julander et al. on brass foundry workers. Based upon their analysis, the authors concluded that hand-to-mouth behaviour resulting in ingestion yielded the highest contribution (16 ug/dL BLL), followed by skin absorption (3.3-6.3 ug/dL BLL) and inhalation (2 ug/dL BLL). Therefore, skin absorption of inorganic lead and its contribution to systemic dose needs to be considered (Julander et al., 2020).

Conclusion

Low blood lead levels (BLL) (<5 ug/dL) have been associated with detrimental effects such as cardiovascular issues, renal dysfunction, genotoxicity, and hematological problems. Lead can be absorbed through inhalation, ingestion and skin contact, with ingestion being the primary route. The Centers for Disease Control and Prevention (CDC) has established that any exposure to lead can cause adverse health effects, with a BLL of >5 ug/dL regarded as elevated in both children and adults, leading to a recommendation of a BLL of <5 ug/dL. The Australian Institute of Occupational Hygienists (AIOH) recommends a BLL of <5 ug/dL for females of reproductive age. Numerous health institutions consider a BLL of 5 ug/dL or higher to be elevated and requiring

clinical intervention. To ensure adequate protection of workers, we recommend the ACGIH ® BEI ® be lowered to 5 ug/dL (or 50 ug/L).

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Date Submitted March 31, 2023

Chemical Substance **Nickel and nickel compounds except Nickel carbonyl**
(8 pages + citable materials)

Name of Group/Individual Submitting Comments Occupational Health Clinics for Ontario Workers Inc. (OHCOW)
Authored by: Kevin Hedges, PhD, MAppSc, BSc, DipEd, COH, CIH
Reviewed by: Krista Thompson, MHSc, ROH, CRSP Occupational Hygienist, Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP Executive Director

Contact Information

Address 1090 Don Mills Road, Suite 606
Toronto, ON M3C 3R6
Canada

Telephone: 416-510-8713 Email: Koconnell@ohcow.on.ca

Executive Summary *(limit 250 words)*

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 TLV® should be applied. With additional supporting information around health effects including cancer, reproductive toxicity, and pneumoconiosis / fibrosis, we recommended the ACGIH TLV®-TWA be reduced from 0.1 to 0.01mg/m^3 for inhalable nickel, applied to soluble and sparingly soluble nickel.

Assigning one limit as 0.01 mg/m^3 for inhalable nickel and compounds (both sparingly soluble and soluble) should be protective for fibrosis.

Due to reproductive toxicity of nickel compounds, biological monitoring (of exposure) is recommended as this will go hand in hand with personal exposure monitoring. A biological exposure index of 10 µg/ L is recommended for mixed nickel species in line with AIOH 2016. 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).

Chemical Substance: Nickel and Nickel compounds except nickel carbonyl

Contact Name: Krista Thompson (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*): see below

Specific Action Requested

1. We recommend one TLV®-TWA for nickel and nickel compounds measured as inhalable nickel as 0.01 mg/m^3 for both soluble and sparingly soluble nickel including mixed nickel species.
2. Due to the carcinogenicity of nickel and mixed nickel species and reproductive toxicity, we recommend inclusion of the abbreviation (L) "exposure to all routes should be carefully controlled to levels as low as possible."
3. Due to the sensitizing health effects, we recommend inclusion in the notations DSEN (dermal sensitization) and RSEN (respiratory sensitization).
4. We recommend a BEI® for nickel in urine at 10 µg/L.

Rationale

Updated information.

- On 16 March 2022, the EU Commission published Directive (EU) 2022/431. **Nickel and its compounds:** Compounds containing nickel are classified as carcinogens (category 1A). As a result, a limit value of 0.01 mg/m^3 is introduced for the respirable fraction, and a limit value of 0.05 mg/m^3 for the inhalable fraction. In addition, the amendment notes that nickel and its compounds can result in dermal and respiratory sensitization.

As noted, OHCOW recommends that the ACGIH adopt one single limit based on inhalable nickel 0.01 mg/m^3 for both soluble and sparingly soluble nickel, and mixed nickel species.

- With regard to biological monitoring, "U-Ni was determined in 19 studies. Limit values were exceeded in 8 studies among industry workers performing incineration operations, flux cored arc welding, stainless steel grinding, and electroplating, and also among workers performing prosthesis preparation. The highest level of U-Ni measured (12.12 ± 8.31 µg/g creatinine) was observed in workers performing incineration operations and other related activities for more than 3 months and for less than 8 months, in a hazard waste incinerator. The lowest levels of U-Ni levels (0.25 µg/g creatinine) were detected among workers in the production, polishing and shaving of stainless-steel vessels and other metallurgical processes at an iron and steel industry" (Tavares et al. 2022).

Rationale for TLV®

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 nickel refinery workers and 336 non-nickel workers. They show pregnancy complications in Ni refinery compared with other workers, and malformations among the specific nickel refinery occupations and non-nickel 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 evidence in humans that nickel is transferred across the placenta, it seems prudent to classify water-soluble nickel compounds as if they cause developmental toxicity. Previous studies of nickel exposure have demonstrated an increased risk to the fetus including spontaneous abortion and birth defects (Chashschin et al. 1994).

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 in biological monitoring.

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 $\leq$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 Ni^{2+} ions at target sites within epithelial cells. The bioavailability of Ni^{2+} 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).

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) analysed 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/m^3–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/m^3 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/m^3 nickel sub sulfide, were similar to those observed with an exposure of 0.11 mg/m^3 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 of 0.06 to 0.03 mg Ni/m^3, resulting in a significant increase 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 sulfate 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 subsulfide (NTP 1996b) at 0.11 mg Ni/m^3 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 exposure 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 Ni_3S_2 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 characterizing particle size and toxicity based on particle size. 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 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). 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 (nano particle) size < 0.1 µm (ECHA 2018, NiPERA 2017).

Inhalable DNELs of 0.05 mg Ni/m^3 for all nickel compounds and nickel metal, respectively was proposed based on respiratory and 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, specifically 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).

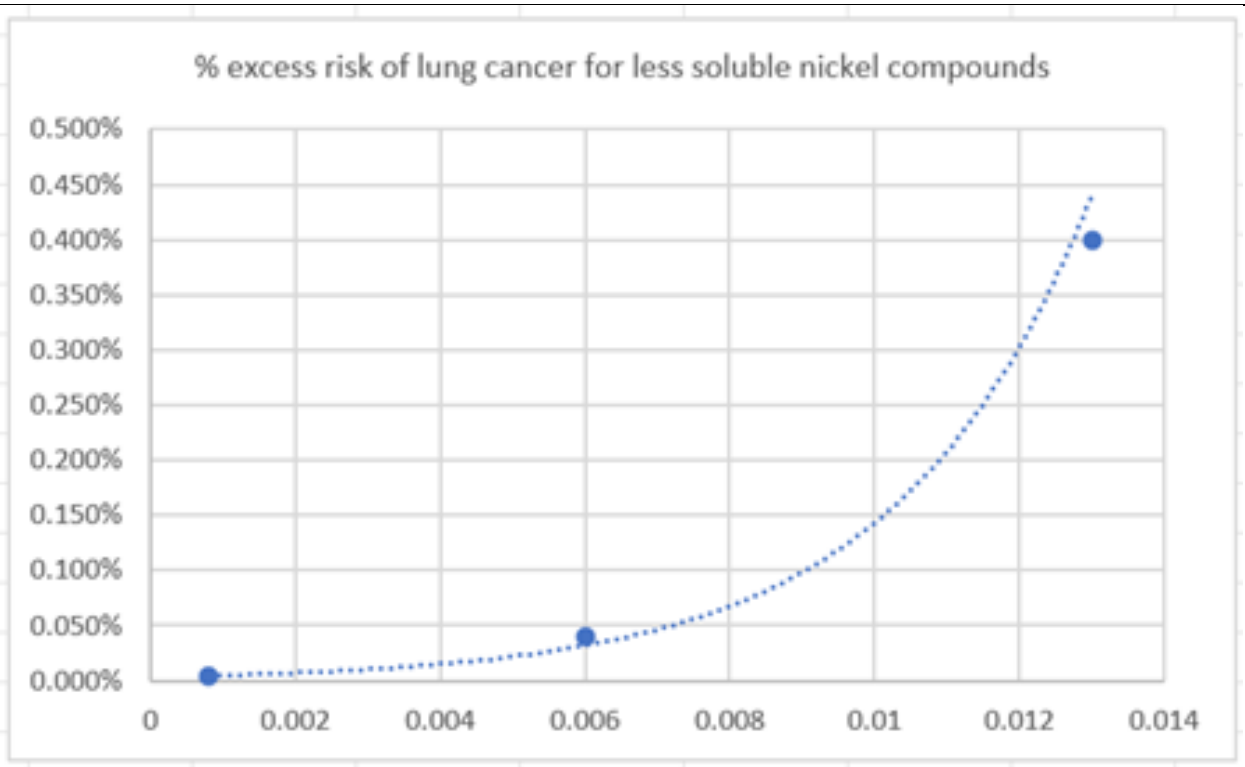

Figure: % excess risk vs. exposure to respirable "less soluble" nickel compounds (Adapted from ECHA 2018).

Lowering the occupational exposure limits for nickel

Occupational exposure limits (OEL) are sometimes defined as sharp boundaries that must not be exceeded (e.g., EU CAD, EU Carcinogens Directive, UK COSHH), and other times as exposure averages, provided short-term exposure limits or excursion limits are not exceeded. 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 exposure averages 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. If technical feasibility is

considered, then that is an important consideration. However, TLV®s can be derived without considering feasibility, and used to drive technical advancements.

Conclusion for TLV®

Setting a TLV®-TWA for inhalable nickel at the level of 0.01 mg/m^3 provides a safety margin to protect against cancer and will reduce the risk from fibrosis and pneumoconiosis when exposed to nickel.

Rationale for BEI®

Biological monitoring of exposure should be considered as being complimentary to personal exposure monitoring. Biological monitoring should be carried out and a BEI® of 10 ug/L in urine is 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 nickel 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 (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/m^3 (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 sulfate) 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" over time could help to drive improvement in exposure to nickel. The study demonstrated positive correlations between hand contamination and biological monitoring results that show that dermal exposure is a significant factor (Beattie et al. 2017).

Biological monitoring of workplace exposure to poorly soluble nickel compounds is essential due to the potential carcinogenic effect of poorly soluble nickel 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 nickel 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.

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 BEI® 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).

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 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. 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, as noted, 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/m^3 exposure was equivalent to 10 μg /L in urine. This provides the rationale for assigning a BEI® of 10 μg/L in urine.

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Date Submitted March 31, 2023

Chemical Substance **Stoddard Solvent**
(3 pages + citable materials)

Name of Group/Individual Submitting Comments Occupational Health Clinics for Ontario Workers Inc. (OHCOW)
Authored by: Krista Thompson, MHSc, ROH, CRSP Occupational Hygienist
Reviewed by: Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP Executive Director

Contact Information

Address 1090 Don Mills Road, Suite 606
Toronto, ON M3C 3R6
Canada

Telephone: 416-510-8713 Email: Koconnell@ohcow.on.ca

Executive Summary *(limit 250 words)*

We recommend a TLV®-TWA of 20 ppm. One study found adverse health effects at an estimated average exposure in paint of 40 ppm (*Lindström and Wickström 1983*), which was not cited in the Stoddard solvent documentation (available at: https://www.acgih.org/stoddard-solvent/). It is noted that this is an imperfect study, as the exposure average was estimated, and the painters had other solvent exposures. In addition, a study by Järnberg et al (*1997*) exposed volunteers to 50 ppm for 2 hours, and did not result in irritation or CNS effects. A study published by Lammers et al (*2007*) compared volunteers exposed to 10 ppm then to 100 ppm, both for 4 hours, spaced 7 days apart. No irritation or CNS effects were observed with 10 ppm exposure, but effects were observed at 100 ppm. A study by Ernstgård et al (*2009*) observed irritation in volunteers exposed to 50 ppm Stoddard solvent for 4 hours, but not in 16 ppm Stoddard solvent, nor clean air.

Chemical Substance: Stoddard Solvent

Contact Name: Krista Thompson (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*): see below

Specific Action Requested

1. We recommend a TLV®-TWA of 20 ppm.

Rationale

Stoddard solvent is also known as mineral spirits, naptha safety solvent, petroleum solvent, white spirits, and products with the trade names Texsolve S and Varsol 1. Stoddard solvent is a petroleum distillate that has many industrial uses, including as a dry-cleaning agent, degreaser, paint thinner, in some photocopier toners, in printing inks, and in adhesives (*Wypych, ed., 2019*). Benzene is a trace impurity in stoddard solvent that typically contained <0.1% benzene since 1975 (*Carpenter 1975, Kalnas and Teitelbaum 2000, Kopstein 2011, NIOSH 1977, William et al 2008*), with additional refinements in the year 2000 resulting in even lower amounts ranging from 0.0002 to 0.09% benzene (*Fedoruk et al 2003, Williams et al 2008*). Benzene is not typically listed on the SDS since concentrations are below the reporting requirement of 0.1%. However, given the range of concentrations and vaporizations, there is no correlation between benzene concentration and airborne exposure relative to Stoddard solvent airborne exposure.

The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European commission recommended an 8-hour occupational exposure limit (OEL) of 20 ppm to prevent nervous system effects, and a short-term exposure limit (STEL) of 50 ppm to prevent acute irritation and acute neurological symptoms (*SCOEL 2007*). The SCOEL OEL was based on a study Lindström and Wickström (*1983*), which compared 219 house painters exposed to an average of 40 ppm Stoddard solvent, compared to 229 unexposed reinforcement workers. This study demonstrated a reduction in testing in exposed workers, particularly in performance in simple reaction time and short-term visual memory tests (*Lindström and Wickström 1983*). Ultimately, SCOEL applied a safety factor of 2 to establish an OEL of 20 ppm.

Safe Work Australia (SWA) has a recommended workplace exposure standard (WES) for stoddard solvent (referred to as mineral spirits): a time-weighted average (TWA) of 50 ppm, and a short-term exposure limit (STEL) of 100 ppm (*SWA 2020*). The WES-TWA is based on irritation, central nervous system (CNS) impairment, and brain damage. The WES-STEL is based on acute irritation, nausea, and CNS depression. These recommended WES are in draft form, and have not been adopted. The reason presented by SWA (*2020*) for the WES-TWA of 50 ppm and WES-STEL of 100 ppm is eight acute volunteer inhalational studies published in the Deutsche Forschungsgemeinschaft (DFG) Maximale Arbeitsplatz-konzentration (MAK) documentation for Stoddard solvent (referred to as hydrotreated heavy naphtha (petroleum)) (*DFG 2010*). Notably the DFG MAK for Stoddard solvent is 100 ppm.

Of the studies cited by SWA (*2020*) and DFG (*2010*), there were three studies published since 1997 that were not previously considered by the ACGIH and that warrant further discussion: studies by Järnberg et al (*1997*), Lammers et al (2007*),* and Enstgård et al (*2009*).

A study published in 1997 observed that exposure to 50 ppm Stoddard solvent for 2 hours did not result in any irritation or CNS effects in 9 male volunteers (*Järnberg et al 1997*). Notably this study was not done for a full 8-hours.

A study published in by Lammers et al (*2007*) investigated exposure to Stoddard solvent on two occasions, with the 12 male volunteers exposed to 10 ppm Stoddard solvent and 100 ppm Stoddard solvent, spaced 7 days apart. No irritation or CNS effects were reported when volunteers were exposed to 10 ppm Stoddard solvent for 4 hours. CNS effects were reported and observed when volunteers were exposed to 100 Stoddard solvent for 4 hours, specifically for: increased fatigue, decreased vigour, finger tapping with dominant hand (but not non-dominanent hand), and greater latency in attention in both simple reaction time and colour word vigilance tests (*Lammers et al 2007*). Some of the effects were deemed "subtle" in terms of magnitude of effect, but still statistically significant when analyzed with a test of significance. Notably the authors conclude the differences in simple reaction time test was more consistently related to exposure, by comparing the results for 10 ppm exposure to 100 ppm exposure. Although the duration was not 8-hours, it still shows that 4-hours of exposure to the current TLV®-TWA can result in adverse health effects.

The study by Ernstgård et al (*2009*) assessed investigated exposure to Stoddard solvent using 6 male and 6 female volunteers exposed for 4 hours, exposed to 16 ppm of Stoddard solvent with 19% aromatics (Stoddard solvent is typically 10-20% aromatics), 50 ppm of Stoddard solvent with 19% aromatics, and clean air. This review is focused on different metrics of irritation. The only significant increases in irritation in exposed compared to unexposed clean air were: 50 ppm Stoddard solvent with 19% aromatics (eye irritation), but not in 16 ppm Stoddard solvent with 19% aromatics (Ernstgård et al 2009). Notably, white spirit with lower percent aromatics were also included, but did not result in irritation.

These studies indicate there are irritation effects at 100 ppm exposure to Stoddard solvent, even at 50 ppm exposure. It is recommended that a TLV®-TWA of 20 ppm be adopted, in line with the study published by Lindström and Wickström (*1983*) and a safety factor of 2. Notably, the study by Lindström and Wickström (*1983*) was not cited in the Stoddard solvent summary published by ACGIH (available at: https://www.acgih.org/stoddard-solvent/). It is noted that this was an imperfect study, as the exposure average was used, and the painters likely had other solvent exposures. If this study is rejected for these reasons, then the study identifying health effects occurring at 50 ppm still warrant consideration (*Enstgård et al 2009*).

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Date Submitted: March 31, 2023

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

Name of Group/Individual Submitting Comments: Occupational Health Clinic for Ontario Workers Inc. (OHCOW)
Authored by: Masood Ahmed MS, CIH, CRSP Occupational Hygienist
Reviewed by: Kimberly O'Connell, M.Sc.(A), CIH, ROH, CRSP Executive Director

Contact Information

Address 1545 Carling Ave. Suite 110

Ottawa, ON K1Z 8P9

Telephone: 613-859-6990 Email: koconnell@ohcow.on.ca

Executive Summary *(limit 250 words)*

There are a large number of workers globally who are exposed directly and indirectly to welding fumes. According to one estimate there are 11 million welders in the world and approximately 1 million in North America [3]. This is likely be an underestimate since many countries do not have a robust human resource database nor are indirectly exposed workers' to welding fume usually 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: Krista Thompson (OHCOW)

Citable Material Attached (*include Permission to Use if necessary*): see below

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 a 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, and 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 the intensity of 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, based on the retrospective exposures from 1961-2001. This amounts to 1.3% lung cancer cases and 5.4% of ocular melanomas diagnosed annually from welding fumes. 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 necessary that a strategy is developed to lower welders' exposure to welding fumes. Therefore, we are making an attempt 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 the ACGIH TLV®s. It was found that the welders had high incidence of bronchitis and pneumonia as compared with the 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 experienced 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 exposures are associated with adult onset of asthma.[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. There 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. [13,14]

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), found that the 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]

Koh et al (2015) studied the relationship between welding fume exposure and Chronic Obstructive Pulmonary Disease in welders at two shipyards in Korea. 240 welders participated in the study by going through a medical examination and filling out health and occupational history questionnaires. The pulmonary function test was performed by qualified staff with strict quality control measures which is different from many other similar studies. 884 total welding fume sampling results were used from 2002 to 2009 to run the multiple linear and logistic regression models to understand the association between COPD and welding exposure. The exposures were grouped into low (0.1-3.4 mg/m^3), medium (3.4-11.7 mg/m^3), and high (11.7-22.8 mg/m^3) and odds ratio (OD) for COPD were calculated for each group. The OD for medium and high exposure groups were significantly elevated i.e. 3.9 and 3.8 respectively as compared with low exposure group. The overall average exposure for an average of 15 years exposure was 7.7 mg/m^3-years which equates to an average welding fume exposure level of 0.5 mg/m^3.[23]

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	≤ 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
Koh et al (2015)	COPD	0.4

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 sample sizes in the studies mentioned in table 1 show the level of rigor in determining an exposure level linked to an adverse health effect. Because of the robustness of the studies, one 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 for 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 risk of exposure and 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, therefore, 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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