MINERALS COUNCIL OF AUSTRALIA

SUBMISSION ON SAFE WORK AUSTRALIA WORKPLACE EXPOSURE STANDARDS REVIEW – SELECTED SUBSTANCES FROM RELEASES 2 TO 14

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1. EXECUTIVE SUMMARY

The Minerals Council of Australia (MCA) appreciates the opportunity to comment on selected Safe Work Australia (SWA) airborne contaminants workplace exposure standards (WESs) covering releases 2 to 14.[1] The specific WESs commented on are limited to airborne contaminants commonly encountered in the workplace of MCA members, for which controls are provided.

As requested by SWA, the feedback focuses on comments of a technical nature regarding the toxicological information and data that the value is based upon, and measurement and analysis information provided.

The submission does not cover the practicality and cost to industry of complying with the proposed WES values. The MCA has specific concerns for the practicality and cost of implementation of some of the proposed WESs and may provide further comment on these aspects in a subsequent submission.

MCA recommends that SWA conduct a phased implementation of any new WES with prioritisation informed by the highest materiality associated with the existing WES. Further, consideration for the timing of any new WES needs to account for establishing baselines, assessing gaps and development and implementation of exposure reduction plans. This work will take time to complete as some of the substances under review are currently not routinely monitored (as the levels are well below the existing WES). It is also possible that with some agents the magnitude of reduction required under the new WES may not be technically feasible to achieve.

The key consideration from a compliance and monitoring perspective is whether the contaminant can be accurately measured at levels well below the proposed WESs, not whether the proposed WESs are measurable. When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission 2017 document 'Methodology for derivation of occupational exposure limits of chemical agents' states that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA.' The use of an action limit (e.g. half the WES) and application of a reduction factor due to extended or unusual shifts (> 8-h day / 40-hour week) would further complicate quantification of exposure concentrations against some proposed WESs. If a substance exposure concentration cannot be meaningfully compared to a WES (adjusted or otherwise) due to results being below the analytical method limit of quantitation, then the exposure data is likely to be perceived as being of little value to drive exposure controls other than the provision of respiratory protection.

The MCA questions the need for a regulatory exposure limit (WES) for a substance with irritation as the primary health effect and with warning properties. Any change in such a WES should take into consideration current toxicological data and severity of associated health outcomes. However, the MCA:

- Agrees that further study/review is required to determine an appropriate WES for both soluble and insoluble forms of aluminium, for arsenic and soluble compounds, and for fluorides, but agrees with both the arsenic and fluorides WESs as suggested
- Supports the proposed change to the WES for ammonia, benzene, cadmium and compounds (as Cd), cyanides (as CN), hydrogen cyanide (HCN – except that a short-term exposure limit (STEL) value of 5 mg/m^3 is more appropriate than the proposed peak value) and nickel metal and insoluble compounds
- Suggests that the beryllium time-weighted average (TWA) WES take into account different toxicity levels depending on whether the beryllium is soluble or insoluble, as well as measurability, adopting the OSHA limit value in the interim

[1] WESs are also termed occupational exposure limits (OELs).

- Believes that the recommended WES reduction for borate compounds from 1 to 0.75 mg/m^3 (as B) is not justified
- Does not support the removal of the current 12,500 ppm carbon dioxide (CO_2) TWA-WES value for coal mines without further consultation
- Agrees with a reduction of the carbon monoxide (CO) TWA-WES, but believe that the ACGIH TWA of 25 ppm may be more appropriate
- Considers that a TWA-WES of 2 ppm rather than 1 ppm is probably most appropriate for carbon disulfide (CS_2) potential exposures
- Considers that a TWA-WES of 0.5 ppm rather than 0.1 ppm would be sufficiently protective for chlorine exposures
- Believes that the interim TWA-WES for chromium II, III and metal (as Cr) should remain at 0.5 mg/m^3 until further review is conducted
- Believes that the recommended TWA-WES for chromium VI cannot be measured using current analytical methods and that the OSHA limit value be adopted in the interim
- Prefers that the AIOH recommendations for coal tar pitch volatiles and for diesel particulate matter (DPM) be used
- Prefers that there are separate WESs for copper fume (0.05 mg/m^3 respirable fraction) and copper dust and mist (0.1 mg/m^3 inhalable fraction)
- Agrees with increasing the current WES for hexane to 50 ppm
- Believes that a hydrogen fluoride (HF) TWA-WES of 1 ppm and a STEL of 3 ppm would be sufficiently protective of health and irritation for the majority of workers
- Believes that a hydrogen sulfide TWA-WES of between 1 to 5 ppm and a STEL of between 5 to 10 ppm would be sufficiently protective of health and irritation for the majority of workers, depending upon measurability
- Does not agree that further study involving a review of the available carcinogenicity data for iron oxides is required (such review has already been undertaken and the determination is that iron oxides are not human carcinogens) and believe that the proposed TWA-WES value of 5 mg/m^3 for the respirable fraction should be maintained
- Believes that the WES for isocyanates should be based on preventing the sensitisation of workers, and if this is the case, then the current WES may be sufficiently protective, particularly where medical surveillance is also required to detect susceptible / sensitised individuals
- Suggests that the SCOEL (2011) recommended exposure limits of 0.05 mg/m^3 (respirable fraction) and 0.2 mg/m^3 (inhalable fraction) would be more appropriate WESs for manganese and its compounds
- Suggests that the SCOEL (2014) recommended exposure limits of a TWA of 0.5 ppm and a STEL of 1 ppm would be more appropriate WESs for nitrogen dioxide (NO_2).

The MCA also considers that in some cases where there are complexities in determining toxicity and/or assessing hazardous in-air exposure (e.g. beryllium, coal tar pitch volatiles, DPM, isocyanates), rather than depend on a 'one-size-fits-all' regulatory exposure limit (WES), it would be best to have an industry-specific guidance / best practice approach.

For carcinogens, exposures should be controlled to as low as reasonably practicable (ALARP) and medical surveillance should be provided. In addition, where skin absorption or hand to mouth contamination is an issue (e.g. arsenic, benzene, cadmium, carbon disulfide, carbon monoxide), and

where there are validated biological indicators of exposure, then biological monitoring should be undertaken as a part of a medical surveillance program. This can also serve to check on the efficacy of controls.

2. ALUMINIUM DUSTS AND COMPOUNDS

SWA recommends that the TWA-WES for aluminium – dusts (metal, pyro, oxide) and compounds (soluble, alkyls) be reduced from 10 mg/m^3 to 1 mg/m^3, as an interim value. This revision aims to protect against effects in the lungs and central nervous system (CNS) in exposed workers. It is consistent with the TWA TLV® that the American Conference of Governmental Industrial Hygienists (ACGIH, 2018) recommends.

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.' Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Most of the Western world has set a TWA exposure limit for aluminium (metal & oxide) of between 3 and 10 mg/m^3 for the inhalable fraction and between 0.5 and 6 mg/m^3 for the respirable fraction, as per the Gestis database for international limit values. For aluminium alkyl compounds, the most common exposure limit is 2 mg/m^3.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to insoluble aluminium forms (including aluminium metal, aluminium oxide, bauxite ore dust and emery dust) are considered to be pneumoconiosis, lower respiratory tract irritation and neurotoxicity.

The ACGIH TLV-TWA of 1 mg/m^3 recommendation was based on subtle neurological effects from the inhalation of 1.6 mg/m^3 for 40 years. In essence, this was derived from Sjogren and Elinder (1992), who reviewed a number of studies of aluminium welders and found the frequency and severity of psychomotor abnormalities increased with years of exposure, supporting the concept of cumulative toxicity. Among the studies reviewed in Sjogren and Elinder, workers with an average of 40 years of exposure at an average of 1.6 mg/m^3 (based on an estimate from urinary levels of aluminium) had an increased prevalence of nervous system effects. Rossbach et al (2006) however found that there were no close relationships between dust exposure, aluminium in plasma and aluminium in urine for groups of aluminium welders. In addition, Kiesswetter et al (2009) found no changes in neurobehavioral parameters or motor performance due to aluminium welding in the automobile industry for workers of similar average age, albeit exposed to low dust concentrations (median likely < 1 mg/m^3).

Aluminium is not considered to be a causal factor in Alzheimer's disease. A meta-analysis by Virk & Eslick (2015) did not support a causative role of aluminium in the pathogenesis of Alzheimer's Disease. Lidsky (2014), in considering the published research concerning aluminium's role in Alzheimer's Disease, concludes that not one of the four Bradford Hill criteria deemed necessary to establish causation with respect to neurocognitive disorders has been satisfied. Furthermore, the four remaining criteria, dependent on satisfaction of the four necessary criteria, are also not met. Klotz et al (2017) conclude that aluminium encephalopathy is a distinct disease entity and is not the same as Alzheimer-type dementia.

Klotz et al (2017), in a review article on the health effects of aluminium exposure, note that for aluminium welders and workers in the aluminium industry, declining performance in neuropsychological tests (attention, learning, memory) has been found only with aluminium concentrations exceeding 100 µg/g creatinine in urine (120 µg/L). There is the possibility of using a biological exposure indices.

An asthma-like syndrome has been recognised in aluminium smelter workers for over 70 years, but the causal agent has been difficult to identify. The ACGIH documentation refers to:

- Six new cases of asthma reported in aluminium refinery workers (no number subjects provided) exposed to 2.6 - 5.5 mg/m^3 following an AlF_3 leak (no duration specified), and a sharp decline in number of new asthma cases when concentrations were reduced to 0.4 - 1.0 mg/m^3
- A study of employees of 3 alumina refineries exposed to 0.98 - 2.18 mg/m^3 Al_2O_3 (4-h weighted average) reported no associated significant adverse respiratory effects.

However, fluoride, inhalable dust and sulphur dioxide (SO_2) are considered the most important airborne contaminants associated with effects on lung function in aluminium smelters. In fact, Abramson et al (2010) found that SO_2 was more likely than fluoride to be primarily responsible for wheeze and chest tightness, the two symptoms most closely related to asthma. Van Rooy et al (2011) investigated exposures, respiratory symptoms, lung function and exposure–response relationships among aluminium cast-house workers. While this epidemiological study could not demonstrate exposure-response relationships, it did support preventive measures in the work environment, with a focus on (peak) exposures to irritants.

Beach et al (2001), using data collected from employees at three bauxite mines in Australia, found little evidence of a serious adverse effect on respiratory health associated with exposure to bauxite in an open-cut bauxite mine in present day conditions. Data was derived from participation in a survey comprising: questionnaire on demographic details, respiratory symptoms, and work history; skin prick tests for four common aeroallergens; and spirometry. Dennekamp et al (2015) investigated respiratory health in relation to respirable bauxite dust exposure longitudinally over a 13-year period among bauxite exposed workers in Western Australia. They concluded that increasing exposure to bauxite dust in the aluminium industry was not associated with respiratory symptoms or consistent decrements in lung function.

Willhite et al (2014) note that aluminium is a ubiquitous substance encountered both naturally (as the third most abundant element) and intentionally (used in water, foods, pharmaceuticals, and vaccines). They also note that existing data underscore the importance of aluminium physical and chemical forms in relation to its uptake, accumulation and systemic bioavailability. The toxicity of different aluminium forms depends in large measure on their physical behaviour and relative solubility in water. The toxicity of soluble aluminium forms depends upon the delivered dose of trivalent aluminium (Al(+3)) to target tissues. In contrast, the toxicity of the insoluble aluminium oxides depends primarily on their behaviour as particulates.

SWA assigned the one WES-TWA value for all aluminium compounds, despite different toxicities dependent on solubility. Insoluble forms are poorly absorbed and readily cleared from the lungs by mucociliary and bronchoalveolar activity. Toxicological data for soluble compounds is considered inadequate. In addition, SWA have not defined whether the WES is based on the inhalable or the respirable fraction.

The SWA documentation recommends review of additional data sources be undertaken at the next scheduled review for soluble aluminium compounds due to insufficient data on identified dose-response relationships.

MCA Recommendation

Considering the above data, the MCA agrees that further study is required to determine an appropriate TWA-WES for both soluble and insoluble forms of aluminium. In the interim, the AIOH (2016a) dusts not otherwise specified (NOS) trigger TWA values could be used: 5 mg/m^3 for the inhalable fraction and 1 mg/m^3 for the respirable fraction. Alternatively, the DFG (2015) aluminium- [7429-90-5], aluminium oxide- [1344-28-1; 1302-74-5] and aluminium hydroxide- [21645-51-2] containing dusts MAK values of 1.5 mg/m^3 (respirable) and 4 mg/m^3 (inhalable) could be used.

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3. AMMONIA

SWA recommends that the TWA-WES for ammonia be reduced from 25 ppm to 20 ppm, to protect against eye and respiratory tract irritation in exposed workers. The previous short-term exposure limit (STEL) of 35 ppm has been retained, to protect against acute exposures and minimise irritation effects and discomfort.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Most of the Western world has set a TWA exposure limit for ammonia of between 10 and 50 ppm, as per the Gestis database for international limit values, with most (57%) being set at 20 ppm. STEL values of between 20 and 50 ppm are used, with most (50%) being set at 50 ppm, although 33 percent are set at 35 ppm.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to ammonia are irritant effects of the eyes and respiratory tract. The ACGIH (2018) cite references that support irritant effects down to 20 ppm. They have assigned a TLV-TWA of 25 ppm (17 mg/m^3) and a TLV-STEL of 35 ppm (24 mg/m^3) for ammonia. SCOEL (1992) note a lowest observed adverse effect level (LOAEL) of 50 ppm (36 mg/m^3) for mild irritation, reported in humans. They have assigned a TWA value 20 ppm (14 mg/m^3), derived by applying an uncertainty factor to the LOAEL, and a STEL of 50 ppm (36 mg/m^3). They further note that long-term exposure to 10 ppm produced no effects in workers. The DFG (2015) also maintain a MAK TWA of 20 ppm.

Ammonia solution, with more than 10 percent but not more than 35 percent ammonia appears as a colourless aqueous liquid solution with a strong odour of ammonia. Both liquid and vapours are extremely irritating, especially to the eyes (PubChem). ATSDR (2004) states that ammonia has a very strong odour that is irritating and that you can smell when it is in the air at a level higher than 5 ppm. They further state that 'you will probably smell ammonia before you are exposed to a concentration that may harm you.'

A recent study by Mahdinia et al (2020) notes that exposure to ammonia lower than the ACGIH TLV can act as a risk factor of respiratory disorders.

MCA Recommendation

Considering the above data, the MCA supports the proposed change to the TWA-WES, noting that consideration be given to the necessity of a WES for ammonia, if its health effect is primarily irritation, with warning properties. The MCA questions the need for a regulatory exposure limit (WES) for a substance with irritation as the primary health effect and with warning properties. Any change to the WES should take into consideration current toxicological data as well as the severity of associated health outcomes.

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4. ARSENIC AND SOLUBLE COMPOUNDS

SWA recommends that the TWA-WES for arsenic and compounds (except arsine) be reduced from 0.05 mg/m^3 to 0.01 mg/m^3, to protect against excess skin, lung and liver cancers in exposed workers. It is consistent with the TWA TLV® that the American Conference of Governmental Industrial Hygienists (ACGIH, 2018) recommends.

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.' Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA notes that there is uncertainty regarding quantification of the recommended value with currently available sampling and/or analysis techniques.

Most of the Western world has set a TWA exposure limit for arsenic and compounds of between 0.003 and 0.1 mg/m^3, as per the Gestis database for international limit values, with most (64%) being set at 0.01 mg/m^3.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to arsenic compounds is carcinogenicity. Lung cancer is the primary cause of concern with chronic inhalation of inorganic arsenic in the workplace. IARC (2012) consider that there is sufficient evidence in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite and arsenate, cause cancer of the lung, urinary bladder and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver and prostate. An excess of deaths due to respiratory cancer has been observed among workers exposed to inorganic arsenic in the production and use of pesticides, gold mining, and in the smelting of nonferrous metals, especially copper (WHO, 2001).

The ACGIH TWA TLV® is based on an epidemiological study of arsenic exposed workers in which the lowest exposure level associated with an excess risk of lung cancer was 0.2 mg/m^3. As there is not an established 'no effect level' for cancer risk for these compounds, a factor of 20 was applied to account for uncertainties in mutagenicity data and no clear 'no observed adverse effect level' (NOAEL) for carcinogenic effects to derive the TWA value of 0.01 mg/m^3.

A study of copper smelter workers (Lubin et al, 2008) revealed a linear relationship between cumulative inorganic arsenic exposure and respiratory cancer mortality within categories of arsenic concentration. In addition, the study found a direct concentration effect on the exposure-response relationship, indicating that for a fixed level of cumulative arsenic exposure, inhalation of higher concentrations of arsenic over shorter durations was more deleterious than inhalation of lower concentrations over longer durations. It is uncertain as to how this information can contribute to derivation of an exposure limit.

While a 'no effect level' for cancer risk for arsenic compounds has not been established, Lewis et al (2015) state that the mode of action for arsenic supports a carcinogenic threshold. They contrast and compare the analyses conducted by various agencies and critically evaluate strengths and limitations inherent in the data and methodologies used to develop quantitative risk estimates. ECHA (2013) state that the:

> Cancer mode of action of arsenic and its inorganic compounds has not been established, but it appears not to be related to direct DNA reactive genotoxicity and therefore it is possible that the arsenic carcinogenicity has a threshold exposure level. However, the available data do not allow the identification of threshold exposure levels for key events in the modes of action proposed in the scientific literature.

ECHA (2013) derived excess lifetime (up to age 89) lung cancer risk estimates for workers exposed at different 8h-TWA concentrations of inorganic arsenic (inhalable particulate fraction) for 40 years. At 0.01 mg/m^3, a 1,400 excess lung cancer risk in EU workers was calculated – where excess lifetime lung cancer mortality risk = 1.4 x 10^{-4} per µg As/m^3. They note that the dose response relationships were derived by linear extrapolation outside the range of observation, which inevitably introduces uncertainties. Further, as the mechanistic evidence is suggestive of non-linearity, they acknowledge that 'the excess risks in the low exposure range might be an overestimate.'

The molecular aetiology of arsenic-induced cancer remains unclear. Ferragut Cardoso et al (2018) note that recent evidence clearly indicates that gene expression modifications induced by arsenic may involve epigenetic alterations, including miRNA dysregulation, but more research is required to improve our knowledge regarding the mechanisms involved in arsenic-induced carcinogenesis. Huang et al (2019) present findings that offer evidence for illustrating the mechanism of arsenic-related immune dysregulation in the progression of carcinogenesis, noting that only a portion of arsenic-exposed humans eventually develop malignancies, likely attributed to the arsenic-impaired immunity in susceptible individuals. They also note that drinking arsenic-contaminated water is the major route of human exposure.

The possibility of an association between inorganic arsenic exposure and cardiovascular outcomes has received increasing attention in the literature over the past decade. Sidhu et al (2015) conducted a review and evaluation of the animal, mechanistic and human data relevant to the potential mechanism of action of inorganic arsenic in drinking water and cardiovascular disease. Their analysis of the available evidence indicated that there is not a well-established mechanism of action for inorganic arsenic in the development or progression of cardiovascular disease. They conclude that there are no data supporting a linear dose-response relationship between inorganic arsenic and cardiovascular disease, indicating the relationship has a threshold.

The ACGIH (2018) currently recommend a biological exposure indices (BEI) value of 35 µg As/L in urine collected in a spot sample at the end of the work week. The measurements are an indicator of exposure over the work week, and can supplement in-air monitoring results.

ATSDR (2004) states that there is almost no information available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms.

SWA notes that the assessment of arsenic mutagenicity is complicated by the variety of compounds within the arsenic group. SWA recommends that a detailed examination of these data be prioritised during subsequent reviews.

The Environment Agency (2008), a public body protecting and improving the environment in England and Wales, provides a useful overview of the toxicity of arsenic in air.

Comment on measurement and analysis

Inorganic arsenic in particulate collected at a copper smelter using traditional NIOSH methods during 16 sampling events determined concentrations as follows:

- A mean respirable concentration of 0.044 mg/m^3 (range 0.012-0.077 mg/m^3)
- A mean PM_{10} concentration of 0.048 mg/m^3 (range 0.010-0.11 mg/m^3)
- A mean total concentration of 0.049 mg/m^3 (range 0.011-0.10 mg/m^3).

That is, respirable fraction fume dominated the samples. In another publication, arsenic exposures in a copper smelter ranged from 0.0007 to 0.092 mg/m^3, averaging 0.025 mg/m^3.

The Reliable Quantitation Limit (RQL) for arsenic as stated in the OSHA Sampling and Analytical Method number 1006 is around 0.00034 mg/m^3. For NIOSH Analytical Method number 7304, the limit of detection is around the same.

When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission (2017) states that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA.' Both the OSHA and NIOSH analytical methods appear to be able to achieve this for a 0.01 mg/m^3 limit value.

MCA Recommendation

Considering the above data, the MCA supports further review of arsenic WESs but agrees with the WES as suggested. However, considering the carcinogenic effect, exposures should be controlled to as low as reasonably practicable (ALARP), with medical surveillance required in the event of susceptible individuals. Biological monitoring (in urine) is also recommended to take into account dietary arsenic intake as well as to check on the efficacy of controls, primarily respiratory protection and for hand-to-mouth contamination.

SWA also needs to clarify quantification of the recommended value with currently available sampling and analysis techniques in Australia.

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5. BENZENE

SWA recommends that the TWA-WES for benzene be 0.2 ppm (0.7 mg/m^3) rather than 1 ppm, to reduce the risk of leukaemia and other adverse effects in exposed workers. It is consistent with the Health Council of the Netherlands (HCOTN, 2014) proposed TWA limit value derived from epidemiological studies involving worker exposure and associated haematotoxicity, genotoxicity and carcinogenicity.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Most of the Western world has set a TWA exposure limit for benzene of between 0.06 and 10 ppm, as per the Gestis database for international limit values, with most (66%) being set at 1 ppm. Some 11 countries have also set a STEL value, ranging from 1 to 5 ppm (2.5 & 5 ppm being equally prominent).

Comment on toxicological information and data

Where possible, the use of benzene in manufacturing processes has been reduced by replacement with less hazardous compounds. Hence, benzene is now generally regarded as almost exclusively a product of petroleum refining. Workers in petroleum refineries, including those involved in loading and transportation of petroleum products, may have some level of exposure to benzene (Edokpolo et al, 2015).

The critical effects in humans that are associated with exposure to benzene is carcinogenicity. Benzene is a known human carcinogen with evidence presented in various epidemiological studies in occupational settings and supported by experimental animal studies of both oral and inhalation routes (IARC, 2018). IARC (2018) conclude that benzene exhibits many of the key characteristics of carcinogens. In particular, there is strong evidence, including in exposed humans, that benzene:

- Is metabolically activated to electrophilic metabolites
- Induces oxidative stress and associated oxidative DNA damage
- Is genotoxic, inducing DNA damage and chromosomal changes
- Is immunosuppressive
- Causes haematotoxicity.

ECHA (2018) derived a limit value of 0.05 ppm for chromosomal damage in bone marrow, taking into account previous reviews by international scientific expert bodies and recent scientific literature focussing on human data and the mode of action of carcinogenicity of benzene (e.g. SCOEL, IARC, ATSDR), as well as reviewing primary literature from the last ten years and earlier in critical areas such as genotoxicity and haematotoxicity.

The key conclusions were that:

- A mode-of-action-based threshold for chromosomal damage in workers can be used to establish an OEL for carcinogenicity
- The limit so derived, will avoid exposures that induce chromosomal damage in workers, is considered to have no significant residual cancer risk and will also avoid other adverse effects
- An extensive human database is available and epidemiological studies of populations occupationally exposed to benzene consistently demonstrate an excess leukaemia cancer risk, in particular for acute myeloid leukaemia
- The major and most sensitive target organs of benzene are the bone marrow and the haematological system. Benzene affects virtually all peripheral blood cell types, as seen by

haematological suppression in workers and experimental animals, due to bone marrow toxicity. An OEL based on chromosomal damage will also avoid exposure causing haematological suppression

- Benzene can be measured in the air at very low concentrations using standardised methods. Considering a substantial dermal uptake of benzene, air measurements can be complemented with urinary measurements of either benzene as such or the metabolite S-phenylmercapturic acid with sampling at the end of exposure or the end of working shift
- Absorption via the dermal route could make a substantial contribution to total body burden, and thus a skin notation is warranted.

The ECHA (2018) study notes that chromosomal damage is reported for benzene-exposed workers with LOAECs estimated for peripheral blood lymphocytes from concentrations of about 1 ppm, and some reports also suggest clastogenic and aneugenic effects below 1 ppm, the most relevant studies showing effects at concentrations of around 0.5 ppm in petroleum refinery workers. In the range below 0.1 ppm, no relevant effects are reported in the more reliable studies reviewed. ECHA applied an 'assessment factor' to account for uncertainties to derive their 0.05 ppm limit value.

SWA notes that there are a range of LOAEL (0.5 ppm to 1 ppm) and NOAEL (0.6 ppm to 0.9 ppm) for the critical effects of haematotoxicity, genotoxicity and carcinogenicity in exposed workers (HCTON, 2014; SCOEL, 1991). To account for uncertainties associated with LOAEL and NOAEL ranges, a factor of three was applied to the lowest value to derive a TWA of 0.2 ppm.

MCA Recommendation

Considering the above data, the MCA agrees with the TWA-WES as suggested. However, considering the carcinogenic effect, exposures should be controlled to as low as reasonably practicable (ALARP) and medical surveillance required, including biological monitoring (in urine), to take into account the potential for skin absorption as well as to check on the efficacy of controls, primarily respiratory protection.

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6. BERYLLIUM AND COMPOUNDS

SWA recommends that the TWA-WES for beryllium and compounds be reduced from 0.002 mg/m^3 (2 µg/m^3) to 0.00002 mg/m^3 (0.02 µg/m^3), with a STEL of 0.0002 mg/m^3 (0.2 µg/m^3), to protect against beryllium sensitisation in exposed workers and consequently to protect for chronic beryllium disease (CBD) in sensitised individuals. This TWA is also expected to protect against potential cancers of the lung and respiratory tract. With evidence to support a link between acute beryllium disease and CBD, SWA also recommends a STEL value to reduce the risk of developing CBD after acute exposures. Both the proposed TWA and STEL values are consistent with the SCOEL (2017) proposed limit values.

SWA notes that there is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques.

Most of the Western world has set a TWA exposure limit for beryllium and compounds of between 0.00005 and 0.002 mg/m^3, as per the Gestis database for international limit values, with most (46%) being set at 0.002 mg/m^3. Some 10 countries have also set a STEL value, ranging from 0.0004 to 0.01 mg/m^3, the latter being most used.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to beryllium are beryllium sensitisation (BeS), chronic beryllium disease (CBD, or berylliosis), an irreversible and sometimes fatal scarring of the lungs, and carcinogenicity (SCOEL, 2017). Under GHS beryllium is classified as being fatal if inhaled, toxic if swallowed, may cause cancer by inhalation, causes damage to organs through prolonged or repeated exposure, causes serious eye irritation, causes skin irritation, may cause an allergic skin reaction and may cause respiratory irritation.

Beryllium is classified as a 'known' human carcinogen by IARC (2012), although this has been challenged (Levy et al, 2007; Levy et al, 2009; Boffetta et al, 2012). Its GHS classification is as a category 1B carcinogen. SCOEL (2017) note that increased mortality from lung cancer has been shown in a number of studies in exposed workers, at concentrations of 0.01 mg/m^3 and higher.

SWA note that there is insufficient data to conclude that the mode of action for carcinogenic effects of beryllium in humans and animals is due to genotoxicity.

Based on aluminium industry experience, a TWA exposure limit of 0.0002 mg/m^3 (as total) is recognised as being safe in the context of primary aluminium production where beryllium compounds are mainly water soluble.

Madl et al (2006) found that the prevalence of CBD and beryllium sensitisation was greatest among workers involved with machining or grinding of beryllium oxide and metal. No cases of CBD have been reported among workers with exclusive exposure to mining or processing of beryllium ore. Differences in the prevalence of CBD involving work with different chemical forms of beryllium appear to be dependent on the type of operation, generation of fine particulate, beryllium dust exposure levels, solubility and bioavailability of the beryllium.

Taiwo et al (2008) found that, when compared with beryllium-exposed workers in other industries, aluminium smelter workers had lower rates of sensitisation (0.27%). Of the sensitised employees, only two received a clinical (no biopsy) diagnosis of CBD upon further evaluation. They conclude that the low beryllium sensitisation rate observed may be related to work practices and the properties of the beryllium found in this work environment.

In another study, Taiwo et al (2010) found that, while aluminium smelter exposure levels to beryllium were similar to those seen in other industries that utilise beryllium, compared with beryllium-exposed workers in other industries, the rate of beryllium sensitisation among aluminium smelter workers appears lower. Nine workers were diagnosed with beryllium sensitisation (prevalence rate of 0.47%, 95% confidence interval = 0.21 - 0.88%). This lower observed rate may be related to a more soluble

form of beryllium found in the aluminium smelting work environment as well as the consistent use of respiratory protection.

In addition, there is evidence for a genetic sensitivity to beryllium (e.g. Kreiss et al, 2016) and a skin component for beryllium sensitisation (Virji et al, 2019). Fireman et al (2014) conclude that biological monitoring is more informative than environmental monitoring in the surveillance and monitoring of workers in beryllium industries.

Virji et al (2019), upon conducting a survey of short-term workers employed at a primary beryllium manufacturing facility, found that the metrics of peak inhalation exposure, indices of skin exposure, and using material containing beryllium salts were significantly associated with skin symptoms and BeS, and skin symptoms were a strong predictor of BeS. They suggest that prevention efforts should focus on controlling airborne beryllium exposures with attention to peaks, use of process characteristics (e.g. the likelihood of upset conditions to design interventions) to minimise skin exposure to beryllium particles, and in particular, eliminate skin contact with beryllium salts to interrupt potential exposure pathways for BeS risk.

After considerable consultation, OSHA issued a final rule (OSHA Standard Number 1915.1024) to prevent chronic beryllium disease and lung cancer, establishing an 8-h TWA exposure limit of 0.0002 mg/m^3 (0.2 $\mu g/m^3$) and a STEL value of 0.002 mg/m^3.

Comment on measurement and analysis

Personal beryllium samples obtained from nine aluminium smelters owned by four different aluminium-producing companies (Taiwo et al, 2010) showed a range of <0.01–13 $\mu g/m^3$ TWA with an arithmetic mean of 0.00025 mg/m^3 (0.25 $\mu g/m^3$).

The RQL for beryllium as stated in the OSHA Sampling and Analytical Method number ID-125 is around 0.00002 mg/m^3, at best. For NIOSH Method number 7304, the limit of detection is around 0.00001 mg/m^3. The measurement technique should be able to assess exposure at 0.1 times the WES for an 8-hour TWA (European Commission, 2017).

The aluminium industry experienced difficulty in finding laboratory facilities within Australasia capable of analysing to the required limit of quantitation (LoQ) to meet the 0.0002 mg/m^3 industry exposure limit. Laboratories in North America were used to meet this limit.

MCA Recommendation

Considering the above data, the MCA suggests that the TWA-WES take into account different toxicity levels depending on whether the beryllium is soluble or insoluble, as well as measurability. In the interim, it would probably make sense to adopt the OSHA limit value as a WES. Certainly, for water soluble beryllium, as found in the aluminium industry, a TWA exposure limit of 0.0002 mg/m^3 (as inhalable) is recommended. In addition, medical surveillance should be required in the event of susceptible individuals.

Given the complex aspects of beryllium toxicity, rather than depend on a 'one-size-fits-all' regulatory exposure limit (WES), the MCA recommends an industry-specific guidance/best practice approach. Such approaches already exist, as follows:

- The IRSST Beryllium Good Practices Guide
- The Materion Interactive Guide to Working Safely with Beryllium.

SWA also needs to clarify quantification of the recommended value with currently available sampling and analysis techniques available in Australia.

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7. BORATE COMPOUNDS

SWA recommends that the TWA-WES for borate compounds (1330-43-4 - sodium borate, anhydrous; 12179-04-3 - sodium borate, pentahydrate; 1303-96-4 - sodium borate, decahydrate; 10043-35-3 - boric acid) be reduced from 1 mg/m^3 to 0.75 mg/m^3 (as boron; B), to protect against irritation of the mucous membranes in exposed workers. The TWA is also expected to reduce the risk of possible reproductive (birth rate) effects in humans.

Separately, SWA recommends an interim TWA of 10 mg/m^3 for boron oxide (CAS No 1303-86-2) to protect against eye and respiratory tract irritation in exposed workers. Given the limited data available from the primary sources, SWA also recommends reviewing additional sources at the next scheduled review.

SWA notes that the recommended values are readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Most of the Western world has set an exposure limit for borate compounds as follows as per the Gestis database for international limit values:

- Disodium tetraborate, decahydrate (CAS No 1303-96-4) – a TWA value of between 0.5 and 5 mg/m^3, with most (53%) being set at 5 mg/m^3; plus, a STEL of between 0.75 to 6 mg/m^3
- Disodium tetraborate, anhydrous (CAS No 1303-43-4) – a TWA value of between 0.5 and 2 mg/m^3, with most (62%) being set at 1 mg/m^3; plus, a STEL of between 0.75 to 6 mg/m^3
- Boron trifluoride (CAS No 7637-07-2) – a TWA value of between 0.83 and 3 mg/m^3, with most at the latter value; plus, an emphasis on a STEL of between 2 to 3 mg/m^3, with most at the latter value
- Boron oxide (CAS No 1303-86-2) – a TWA value of between 1.8 and 15 mg/m^3, with most (88%) being set at 10 mg/m^3; plus, a STEL of between 15 to 20 mg/m^3, with most at the latter value.

Comment on toxicological information and data

SWA notes that the NOAEL for irritant nasal symptoms is reported at 5 mg/m^3 for sodium tetraborate (pentahydrate) which equates to 0.75 mg/m^3 of boron. SWA states that this concentration is considered to be sufficiently low to protect for nasal irritation in exposed workers and is therefore recommended as a TWA for all borate compounds. Further, while the ACGIH (2018) recommend a STEL of 6 mg/m^3, SWA states that there is no evidence the irritation leads to a severe, chronic health effect and little evidence to suggest the irritation as acutely severe or intolerable. Therefore, the TWA is considered protective and a STEL is not recommended.

No major toxicological distinctions between boric acid and its salts are recognised in humans. Boron and its compounds have relatively low acute toxicity, but can be acutely toxic at very high oral doses, resulting in gastrointestinal irritation (vomiting, diarrhoea and nausea) and erythema. Boron dust (as boron oxide and boric acid) causes mild irritation of the nose, eye and throat in humans (Hubbard, 1998). Boron is readily absorbed following oral exposure in both humans and animals. Greater than 90 percent of an orally administered dose of boron as boric acid is excreted in a short time in both humans and in animals. In humans, boron was excreted 92 to 94 percent unchanged in the urine after 96 hours (EPA, 2004).

The only chronic effects of boron in consideration are reproductive and developmental effects. Laboratory studies have shown that large doses of boron compounds can cause reproductive and developmental effects in animals (Price et al, 1998). Epidemiological studies have not confirmed this effect in humans (Şayli, 1998; Tűccur et al, 1998). The relevant doses to humans for this to occur are very high, and cannot be achieved by any reasonable route of intake (Hubbard, 1998). EPA (2004) conclude that while there is a report of testicular effects in a small number of Russian workers

exposed to very high concentrations, there is no evidence of an effect on fertility in a controlled epidemiology study in US borate production workers. Only irritant effects have been associated with borate exposure in US workers, with no evidence of an effect on pulmonary function.

DFG (2015) recommend different MAK values to protect against acute irritant effects as follows, where the boron content is used as the reference:

- 5 mg/m^3 for sodium tetraborate pentahydrate (0.75 mg/m^3 as B)
- 10 mg/m^3 (boric acid, 1.8 mg/m^3 as B)
- 0.75 mg/m^3 (other tetraborates and hydrates as B).

A UK HSE (HSC, 2003) review determined there was limited documentation or the basis of the limit was uncertain for this substance, hence have not provided a workplace exposure limit (WEL) for borates.

The recommended limit value of 0.75 mg/m^3 (as B) was derived by DFG (2015) based on a study addressing respiratory irritation in human volunteers exposed to boric acid or sodium tetraborate pentahydrate during physical activity (Cain et al, 2004, 2008). While no irritation was found among 12 subjects exposed to boric acid concentrations up to the highest test concentration of 10 mg/m^3, leading to the derived no observed adverse effect concentration (NOAEC) of 1.8 mg/m^3 (representing the MAK value for boric acid), DFG (2015) considers a NOAEC of 5 mg/m^3 as point of departure for derivation of the MAK value for sodium tetraborate pentahydrate. This NOAEC value is based on increased nasal secretion observed after 20 minutes of exposure.

However, using nasal secretion as a basis for setting the NOAEC is problematic as discussed in more detail below. In the Cain et al (2004) study, the amount of secretion correlated with area under the curve estimates for chemosensory response, but not irritation. Though, in the Cain et al (2008) study, the correlation was not significant. The nasal secretion response in the absence of reported irritation was not considered adverse in the context of risk assessment by the US EPA (1994). The relationship between nasal secretion and signs of irritation is complex and is not well characterised. Therefore, nasal secretion reported in Cain et al (2004, 2008) should not be a critical aspect, since it is an early physiological response to the physical stimuli captured by the chemesthetic response (Alarie, 1973; Cain et al, 2004; Maier et al, 2014). There is no clear benchmark to irritation other than the intensity rating data, which can be used directly. There is no compelling reason that the exposure limits should be different for these two materials based on Cain's work if 'irritation' prevention is the basis for the limit. Different exposure limits for boric acid and sodium borates do not make sense if the basis is boron content as the mechanism of action.

References are made in DFG (2015) to the Cain et al (2004, 2008) studies of eye, throat and nasal irritation. However, Cain et al clearly noted that participants did not consider exposures of boric acid and sodium borate less than 17 percent carbon dioxide (CO_2) equivalent as being "irritating". The gas CO_2 tingles in the nose and eyes at concentrations as low as 5 to 10 percent, which was considered as "sub-irritating". During the study, subjects registered time-dependent feel from exposures to borates, principally in the nose, secondarily in the throat and hardly in eyes. By rating the feel of exposures in the nose, throat and eye, against reference concentrations of CO_2, subjects can distinguish the combination of time and concentration that produce "sub-irritating" in contrast to "irritating" levels of chemesthetic magnitude.

Therefore, exposures equivalent to less than 17 percent CO_2 were not considered irritating, although the volunteer recognised the presence or "feel" of the particulates. The DFG (2015) justification incorrectly reports levels of feel as equal to irritation. Responses at 10 mg/m^3 did not reach the level considered irritating by study participants. Overall, the data show a dose-response where 5 to 10 mg/m^3 is the range of chemesthesis onset, and 10 to 30 mg/m^3 is the transition to irritation onset. Cain et al (2004) reported that increased nasal secretion was measured at 10 mg/m^3 (1.5 mg B/m^3) sodium tetraborate pentahydrate, but not at 5 mg/m^3 (0.75 mg B/m^3). However, the increased nasal

secretion occurred at concentrations below which volunteers considered irritating. A similar statistically significant increase in secretion was not observed at 10 mg/m^3 in the later study (Cain et al, 2008).

Materials that cause mechanical sensations in mucosal tissue may produce reflex responses as well, including an increase in secretions and blood flow to the tissue (Alarie, 1973; Cain et al, 2004; Maier et al, 2014). The increase in secretion could be mechanical in nature due to the increased particle deposition in the nose rather than a chemesthetic response to sodium borate. A NOAEC for irritation of 10 mg/m^3 of sodium tetraborate pentahydrate among male and female human volunteers under controlled laboratory conditions can be derived from Cain et al (2004). Similarly, a NOAEC for irritation among human volunteers of 10 mg/m^3 of boric acid and sodium borate at 10 mg/m^3 can be derived from the study by Cain et al (2008). Cain et al (2008) clearly state the levels of exposure did not reach the level considered irritating by subjects:

> …the highest levels studied here lay at the edge of where people would agree that feel in the nose becomes irritating, about 17-18 % carbon dioxide. None of the functions actually reached that concentration, though those for 2.5 mg/m^3 calcium oxide and 10 mg/m^3 sodium borate came close.

The new data support limit values higher than the 0.75 mg B/m^3 currently set for disodium tetraborates. Exposures in the range of 1.0 -1.5 mg B/m^3 would not be expected to produce any irritant or systemic effects among the most sensitive in workers based on a derived no effect level (DNEL) of 1.5 mg B/m^3 (REACH Registration dossier for boric acid). This value is also in line with an exposure limit recommended for borate compounds derived by a comprehensive weight-of-evidence approach by Maier et al (2014). In this approach, a broad dataset of relevant toxicological data from animal and human studies were evaluated. Consequently, an exposure limit of 1.4 mg B/m^3 for protection against sensory irritation was derived.

Comment on measurement and analysis

ACGIH (2018) note that sufficient analytical methods for speciation of borate compounds in airborne field samples are not available to enable separation of borate compounds.

MCA Recommendation

Considering the above data, the MCA believes that the recommended WES reduction from 1 to 0.75 mg/m^3 (as B) is not justified. The MCA also questions the need for a regulatory exposure limit (WES) for a substance with irritation as the primary health effect. Any change to the WES should take into consideration current toxicological data as well as the severity of associated health outcomes.

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8. CADMIUM AND COMPOUNDS (as Cd)

SWA recommends that the TWA-WES for cadmium and compounds be reduced from 0.01 mg/m^3 to 0.001 mg/m^3 (1 µg/m^3), to protect against effects on the kidneys in exposed workers. It is consistent with the SCOEL (2017) proposed limit value.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques.

Most of the Western world has set an exposure limit for cadmium and compounds of between 0.001 and 0.05 mg/m^3, as per the Gestis database for international limit values, with most (43%) being set at 0.01 mg/m^3.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to cadmium and its compounds include systemic long-term effects on the kidneys and lung cancer. Acute, high exposures via inhalation are reported to be intensely irritating and to result in severe respiratory effects in humans including metal fume fever (ACGIH, 2018). IARC (2012) consider that there is sufficient evidence in humans for the carcinogenicity of cadmium and its compounds, but as noted by SWA, an epidemiological study found no excess cancer incidence in workers exposed to an estimated cumulative exposure of cadmium corresponding to a 40-year TWA of 21 to 40 mg/m^3. In addition, Sorahan and Esmen (2004) determined from a study of UK nickel-cadmium battery workers that their findings did not support the hypothesis that cadmium compounds are human lung carcinogens! SCOEL (2017) note that cadmium is a carcinogen with a threshold level for effect.

The mechanisms of the systemic toxicity of cadmium are relatively well understood; dose-effect/response relationships are well documented in a number of human studies. The SCOEL (2017) documentation places most emphasis on biological monitoring of cadmium. While the measurement of urinary Cd (Cd-U) reflects the body burden of the element and predicts the health risk, the measurement of blood Cd (Cd-B) may provide complementary information to detect recent exposures and evaluate the impact of preventive measures to control exposure. SCOEL (2017) recommend a biological limit value of 2 µg Cd/g creatinine in urine. The ACGIH (2018) recommend 5 µg Cd/g creatinine in urine and 5 µg/L in blood.

MCA Recommendation

Considering the above data, the MCA agrees with the TWA-WES as suggested, although if set in conjunction with a biological exposure indice (BEI), it could be 0.004 mg/m^3, as proposed by SCOEL. In addition, medical surveillance should be required, including biological monitoring (in urine & blood) to take into account dietary cadmium intake as well as to check on the efficacy of controls, primarily respiratory protection and for hand-to-mouth contamination.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

IARC (2012). Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100C - A *Review of Human Carcinogens: Arsenic, Metals, Fibres and Dusts* – see http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php

SCOEL (2017). *Cadmium and its inorganic compounds - Opinion from the Scientific Committee on Occupational Exposure Limits*. SCOEL/OPIN/336.

Sorahan, T & NA Esmen (2004). Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. *Occup Environ Med, 61*; pp 108-116.

9. CARBON DIOXIDE (CO_2 in coal mines)

SWA does not recommend a separate TWA-WES for coal mines, as there is no available health information to support an independent TWA-WES. SWA recommends the one TWA-WES for carbon dioxide (CO_2) of 5,000 ppm, rather than the additional 12,500 ppm TWA-WES for coal mine CO_2. The STEL of 30,000 ppm remains. Both the TWA value of 5,000 ppm and the STEL of 30,000 ppm were set to protect against physiological changes, metabolic stress and asphyxiation in exposed workers. It is consistent with the ACGIH (2018) proposed limit values.

SWA notes that this value is readily quantifiable through currently available sampling and analysis techniques. However, MCA notes the removal of the 12,500 ppm CO_2 TWA-WES for coal mines is being done without adequate consultation with industry around the effective risk management of this.

Much of the Western world has set an exposure limit for CO_2, with all except Australia having a TWA value of 5,000 ppm, as per the Gestis database for international limit values. The STEL value ranges from 10,000 to 30,000 ppm, with the majority (53%) at 30,000 ppm, although 29 percent use 10,000 ppm.

Comment on toxicological information and data

The critical effect in humans associated with exposure to CO_2 is asphyxiation. SWA notes that CO_2 is produced in the body and has important physiological functions.

Depending on the duration and concentration of CO_2, exposure to high concentrations can produce mild narcotic effects, stimulation of the respiratory centre and asphyxiation. Stimulation of the respiratory centre occurs at 50,000 ppm. A slight effect was reported in submarine personnel exposed continuously to 30,000 ppm with oxygen content maintained at normal concentrations (minimum 18%), while there were no noticeable symptoms reported from exposure to 5,500 ppm for 6 hours (ACGIH, 2018).

The immediately dangerous to life or health (IDLH) CO_2 concentration is considered to be 40,000 ppm.

Guais et al (2011) note that the toxicity of CO_2 has been established for close to a century. Permentier et al (2017) note that studies have shown a wide variability of CO_2 tolerance. Concentrations of fatal cases of CO_2 vary between 141,000 and 260,000 ppm CO_2, and CO_2 tolerance decreases with age. It is also suggested that smokers might have more tolerance due to habituation of higher CO_2 levels in cigarette smoke. At concentrations greater than 50,000 ppm, CO_2 causes the development of hypercapnia and respiratory acidosis. Severe acidosis increases the effects of parasympathetic nervous activity, possibly by interfering with the hydrolysis of acetylcholine by acetylcholinesterase, resulting in a depression of the respiration and the circulation. Concentrations of more than 100,000 ppm CO_2 may cause convulsions, coma and death. CO_2 levels of more than 300,000 ppm act rapidly leading to loss of consciousness in seconds.

NASA's long-duration Spacecraft Maximum Allowable Concentration for CO_2 is 7,000 ppm. Cronyn et al (2012) notes that extensive terrestrial studies support this level as being safe and unlikely to cause adverse health effects. However, they observed the symptoms of headaches, lethargy and moodiness for short-term exposure of astronauts to 5,000 to 6,600 ppm CO_2.

The key effects for setting Emergency and Continuous Exposure Guidance Level (EEGL & CEGL) values are tremor, headache, hyperventilation, visual impairment and CNS impairment (NRC, 2007). Dyspnoea is a commonly reported end-point and can be induced by acute exposures to CO_2 at greater than 30,000 ppm (NRC, 2007). Hyperventilation without dyspnoea occurs at exposure concentrations as low as 10,000 ppm (NRC, 2007). Dyspnoea attributable to CO_2 is aggravated by increasing the level of exertion. The bulk of the data indicate a NOAEL for CO_2 of about 28,000 ppm (for both acute and chronic exposure) on the basis of the findings on dyspnoea and intercostal pain (NRC, 2007). While headaches are commonly associated with increased CO_2 concentrations in

inspired air, there is conflicting data on the concentrations reliably associated with that end point. There may also be an effect of exertion, because CO_2 seems to cause more headaches at lower concentrations during exercise than it does during rest. Concentrations tested ranged from 10,000 to 80,000 ppm and headaches induced by CO_2 seem to be both mild and reversible (NRC, 2007).

It is well established that CO_2 acutely impairs vision and hearing at concentrations exceeding about 25,000 ppm (NRC, 2007). Most studies summarised by the NRC (2007) reported minimal neurobehavioral effects (learning tasks) at CO_2 concentrations between 15,000 to 40,000 ppm with exposure periods of 2 weeks.

At 2,500 ppm CO_2, Satish et al (2012) observed large and statistically significant reductions occurred in seven of nine scales of decision-making performance in office workers, while at 1,000 ppm they observed moderate and statistically significant reductions in six of the nine scales of decision-making performance. They did note however that confirmation of these findings was needed.

Coal mining operations have been operating for decades with a TWA-WES for CO_2 of 12,500 ppm with effective monitoring and controls in place to manage the health of workers.

There are no known cases of CO_2 exposure causing health impacts in the coal mining sector outside of events associated with acute exposures (e.g. from an incident such as a fire). The typical temporary elevated exposures to CO_2 that occur in the mining industry are not known to have caused any health impacts.

The recommendation will have no measurable impact on health and safety outcomes and does not consider the practical impacts and likely significant consequences on the mining industry.

Removal of the coal mine specific WES for CO_2 would render a number of significant underground operations in CO_2 dominated coal seams inoperable, economically unviable and have significant impacts on existing safety practices.

MCA Recommendation

While one TWA-WES of 5,000 ppm for CO_2 might be appropriate for some industries, MCA recommends that SWA retain the separate TWA-WES for coal mines of 12,500 ppm and STEL of 30,000 ppm and conduct a more substantial and meaningful consultation process with the mining sector to assess current risk management processes of CO_2 in underground coal mines.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

Cronyn, PD, S Watkins & DJ Alexander (2012). *Chronic Exposure to Moderately Elevated CO_2 During Long-Duration Space Flight*. Technical Report - National Aeronautics and Space Administration (NASA) – see https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/N20120006045.xhtml

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National Research Council (NRC) (2007). *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants: Volume 1*. Washington, DC: The National Academies Press. https://www.nap.edu/download/11170.

Permentier, K, S Vercammen, S Soetaert & C Schellemans (2017). Carbon dioxide poisoning: A literature review of an often forgotten cause of intoxication in the emergency department. *Int J Emerg Med*, 10(14); see https://intjem.biomedcentral.com/articles/10.1186/s12245-017-0142-y

Satish, U, MJ Mendell, K Shekhar, T Hotchi, D Sullivan, S Streufert & WJ Fisk (2012). Is CO_2 an Indoor Pollutant? Direct Effects of Low-to-Moderate CO_2 Concentrations on Human Decision-Making Performance. *Environ Health Perspect, 120(12)*; pp 1671–1677.

10. CARBON DISULFIDE (CS_2)

SWA recommends that the TWA-WES for carbon disulfide be reduced from 10 ppm (31 mg/m^3) to 1 ppm (3.13 mg/m^3). SWA considers this revised TWA value will protect for the onset of adverse nervous system effects in exposed workers and is protective of other adverse health endpoints including cardiotoxicity. This value is consistent with the TWA TLV® recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2018).

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.'Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA states this value is readily quantifiable through currently available sampling and analysis techniques.

Most of the Western world has set an exposure limit for carbon disulfide of between 1 and 10 ppm, as per the Gestis database for international limit values, with most (48%) being set at 5 ppm.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to carbon disulfide are neurotoxicity and cardiotoxicity. This has been demonstrated in a large range of observational studies, supported by evidence from experimental animal studies for neurotoxicity outcomes. SWA documentation notes that a TWA of 1 ppm was 'considered protective of neurotoxic effects that may begin to develop at 3 ppm.' Using essentially the same documentation, ACGIH (2018) suggest a TWA exposure limit of 1 ppm, while the Dutch (HCOTN, 2011) recommend 2 ppm and SCOEL (2008) recommend 5 ppm.

SCOEL reported various no observable adverse effects level (NOAEL) values for various health endpoints, but say that overall, the threshold/NOAEL for the earliest non-clinical changes appear to be in the range of 3-10 ppm, and this leads to their recommendation of a TWA of 5 ppm. They report that this exposure concentration, which is based on the most subtle neurological and cardiovascular effects, is considered to be protective against the other reported effects, including those on reproductive function.

New Zealand WorkSafe (2019) recommends a TWA-WES of 1 ppm for carbon disulfide. The New Zealand documentation notes that skin penetration resulting in systemic toxicity can occur in workers exposed to carbon disulfide, and the rate of dermal absorption for hands and underarms over 1 hour was calculated to exceed 10 percent of the amount absorbed via the lungs during 8 hours at 2 ppm.

ACGIH (2018) currently recommend a biological exposure indices (BEI) value of 5 µg/g creatinine in urine collected at the end of a shift.

MCA Recommendation

Considering the above data and the fact that a biological exposure indicator value can also be measured, to account for dermal absorption, a TWA-WES of 2 ppm is probably most appropriate. The biological exposure indicator value would need to be consistent with this proposed WES also. In addition, medical surveillance is required, including biological monitoring (in urine), to take into account the potential for skin absorption as well as to check on the efficacy of controls, primarily respiratory protection.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

HCOTN (2011). *Carbon disulfide. Health-based calculated occupational cancer risk values*. The Hague: Health Council of the Netherlands; publication no. 2011/26.

New Zealand WorkSafe (2019). *Workplace Exposure Standard (WES) review – Carbon Disulphide* (CAS NO: 75-15-0). New Zealand Government, May 2019.

SCOEL (2008). *Recommendation from the Scientific Committee on Occupational Exposure Limits for carbon disulfide*. SCOEL/SUM/82.

11. CARBON MONOXIDE

SWA recommends that the TWA-WES for carbon monoxide (CO) be reduced from 30 ppm to 20 ppm, to prevent blood carboxyhaemoglobin (COHb) concentrations in excess of 3.5 percent in exposed workers which in turn will reduce the risk of adverse effects associated with elevated blood COHb levels. SWA considers this revised TWA value will provide a margin of safety for individuals particularly susceptible to the adverse effects of CO exposure including pregnant women and persons with cardiovascular disease. It is consistent with the SCOEL (1995) proposed limit value.

SWA notes that this value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA would agree.

Most of the Western world has set an exposure limit for carbon monoxide of between 17 and 50 ppm, as per the Gestis database for international limit values, with most (41%) being set at 20 ppm.

Comment on toxicological information and data

The critical effect in humans that is associated with exposure to carbon monoxide is its binding to haemoglobin to form carboxyhaemoglobin, thus reducing oxygen uptake.

SWA notes that COHb levels in healthy, unexposed subjects are approximately 0.4 to 0.7 percent. Increase in COHb levels result in adverse health effects with levels greater than 4 percent being associated with adverse health effects in the brain, cardiovascular system and foetuses. Adverse effects on health have been observed in high-risk groups at COHb levels greater than 2 to 3 percent. COHb levels of 5 percent are expected from an adult, undertaking light work, exposed to 35 ppm for 6 to 8 hours (ACGIH, 2018). The ACGIH (2018) TLV-TWA of 25 ppm is intended to maintain blood COHb levels below 3.5 percent, which is their biological exposure indice (BEI) for end of shift.

MCA Recommendation

Considering the above data, the MCA agrees that the TWA-WES should be reduced. However, regarding the intent of the WES to provide a margin of safety for individuals particularly susceptible to the adverse effects CO exposure, much of the minerals industry uses medical surveillance to ensure that such individuals are identified and not exposed to hazardous conditions. As such, the ACGIH TWA of 25 ppm may be more appropriate, particularly given its alignment with the BEI value.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

SCOEL (1995). *Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for carbon monoxide*. SCOEL/SUM/57.

12. CHLORINE (Cl)

SWA recommends that the TWA-WES for chlorine be reduced from 1 ppm to 0.1 ppm, to protect against eye and respiratory tract irritation in exposed workers. They have included a new Peak limitation value of 0.4 ppm to protect against irreversible pulmonary damage, particularly in susceptible individuals. It is consistent with the TWA TLV® that the American Conference of Governmental Industrial Hygienists (ACGIH, 2018) recommends.

SWA notes that this value is readily quantifiable through currently available sampling and analysis techniques.

Most of the Western world has set a TWA exposure limit for chlorine of between 0.3 and 0.5 ppm, as per the Gestis database for international limit values, with most (93%) being set at 0.5 ppm. STEL values of between 0.5 and 1 ppm are used, with most (68%) being set at 0.5 ppm.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to chlorine are eye and respiratory tract irritation and, at higher concentrations, irreversible impairment of lung function.

The recommended TWA is derived from a LOAEL of 0.4 ppm for nasal tissue damage in rats chronically exposed by inhalation. The peak limitation is derived from a NOAEL of 0.4 ppm for lung function impairment reported for volunteers affected by airway hypersensitivity with a corresponding LOAEL of 1 ppm (ACGIH, 2018).

Human data cited by the ACGIH (2018), DFG (2004) and SCOEL (1998) in the SWA documentation note:

- Results from an inhalational study in human volunteers reported a NOAEL of 0.4 ppm and LOAEL of 1 ppm for pulmonary function
- Workers (n=287) presented upper respiratory irritation (78%) for 5-10 d after repeat acute exposures (24-25 over 3-6 months), 58 percent of which were between 0.5 to 8 ppm
- Subjective eye and respiratory tract irritation without lung function impairment noted at 1 ppm (n=8, 2 h), significant irritation occurs at 2 ppm (n=8, 2 h)
- No inflammatory effect to nose or changes in lung function at 0.5 ppm (n=8, 3 h/d, 2 times/d, 3 d)
- Irritation and transient lung function impairment at 1 ppm (4–8 h) in acute inhalational study, with no effects noted at 0.5 ppm (8 h).

The EPA (2016) notes the following effects due to several acute (short-term) studies on humans:

- Tickling of the nose at 0.014 to 0.054 ppm
- Tickling of the throat at 0.04 to 0.097 ppm
- Itching of the nose and cough, stinging, or dryness of the nose and throat at 0.06 to 0.3 ppm
- Burning of the conjunctiva and pain after 15 minutes at 0.35 to 0.72 ppm
- Discomfort ranging from ocular and respiratory irritation to coughing, shortness of breath and headaches above 1.0 ppm - mild mucous membrane irritation at 1 to 3 ppm.

White and Martin (2010) note that acute chlorine exposures can result in symptoms of acute airway obstruction including wheezing, cough, chest tightness and/or dyspnoea, which are fairly nonspecific, and might be present after exposures to a number of inhaled chemical irritants. In humans, the threshold concentration for detection of the odour of chlorine gas ranges from 0.1 to 0.3 ppm. At 1 to 3 ppm, there is mild mucus membrane irritation that can usually be tolerated for about an hour. At 5 to 15 ppm, there is moderate mucus membrane irritation. At 30 ppm and beyond, there is immediate

substernal chest pain, shortness of breath and cough. At approximately 40 to 60 ppm, a toxic pneumonitis and/or acute pulmonary oedema can develop.

ATSDR (2010) states that there were no significant harmful health effects observed in workers exposed for years to relatively low concentrations of chlorine (around 1 ppm).

Comment on measurement and analysis

The quantitative limit for chlorine as stated in the OSHA Sampling and Analytical Method number ID-101 is 0.14 ppm (15-L air sample). Looking at real-time monitoring devices, which are usually used for monitoring chlorine levels, the practical quantitative limit of detection appears to be around 0.1 ppm. The measurement technique should be able to assess exposure at 0.1 times the WES for an 8-hour TWA (European Commission, 2017).

It would appear that the value that SWA recommends is not readily quantifiable through currently available sampling and analysis techniques.

MCA Recommendation

Considering the above data, the MCA believes that a TWA-WES of 0.5 ppm would be sufficiently protective. Given the irritant and warning properties of chlorine, consideration should be given to the necessity of a Peak limitation for chlorine. A STEL of 1 ppm may be more appropriate. The MCA questions the need for a regulatory exposure limit (WES) for a substance with irritation as the primary health effect and with warning properties. Any change to the WES should take into consideration current toxicological data as well as the severity of associated health outcomes.

In addition, SWA also needs to clarify quantification of the recommended value with currently available sampling and analysis techniques.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

ATSDR (2010). *Public Health Statement for Chlorine*. Agency for Toxic Substances & Disease Registry (ATSDR) – see https://www.atsdr.cdc.gov/phs/

Deutsche Forschungsgemeinschaft (DFG) (2004). *Chlorine – MAK value documentation.*

EPA (2016). *Chlorine* – see https://www.epa.gov/sites/production/files/2016-09/documents/chlorine.pdf

European Commission (2017). *Methodology for derivation of occupational exposure limits of chemical agents* - The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL), Luxembourg: Scientific Committee on Occupational Exposure Limits – see https://op.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1

SCOEL (1998). *Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for chlorine*. SCOEL/SUM/76.

White, CW & JG Martin (2010). Chlorine Gas Inhalation - Human Clinical Evidence of Toxicity and Experience in Animal Models. *Proc Am Thorac Soc, 7(4)*; 257-263 – see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136961/

13. CHROMIUM (metal), (II), (III) (as Cr)

SWA recommends that the TWA-WES for chromium (metal, II & III) be reduced from 0.5 mg/m^3 to 0.04 mg/m^3. SWA considers this revised TWA value will minimise irritation and lung effects from chromium (Cr) metal, Cr(II) and Cr(III) compounds in exposed workers. Noting available toxicological data are inconsistent, SWA recommends investigation of additional data sources at the next scheduled review.

SWA notes that this value is readily quantifiable through currently available sampling and analysis techniques.

Most of the Western world has set an exposure limit for chromium (metal, II & III) of between 0.5 and 2 mg/m^3, as per the Gestis database for international limit values, with most (60%) being set at 0.5 mg/m^3.

Comment on toxicological information and data

The ACGIH (2018) recommended TWA-TLV® is based on extrapolation from animal data. SCOEL (2002) note that for chromium III:

> There is evidence from investigations in both animals and man that repeated exposure to concentrations in the region of 0.5 - 2.3 mg Cr(III)/m^3 does not result in adverse effects on the lungs.

MCA Recommendation

Considering the above data and the fact that SWA notes that available toxicological data are inconsistent and recommends investigation of additional data sources, the MCA believes that the interim TWA-WES should remain at 0.5 mg/m^3 until further review is conducted.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

SCOEL (2002). *Recommendation from the Scientific Committee on Occupational Exposure Limits for Chromium Metal, Inorganic Chromium (II) Compounds, and Inorganic Chromium (III) Compounds*. SCOEL/SUM/50.

14. CHROMIUM (VI) (as Cr)

SWA recommends that the TWA-WES for chromium (VI) (hexavalent chromium) be reduced from 0.05 mg/m^3 to 0.000007 mg/m^3 (0.007 µg/m^3). SWA considers this revised TWA value will reduce the risk of cancer in exposed workers, but notes that the available toxicological data are inconsistent and investigation of additional data sources is recommended at the next scheduled review.

SWA does not note any information on whether the recommended value is quantifiable through currently available sampling and analysis techniques.

Most of the Western world has set an exposure limit for chromium VI of between 0.001 and 0.05 mg/m^3, as per the Gestis database for international limit values, with most (47%) being set at 0.05 mg/m^3.

Comment on toxicological information and data

The ACGIH (SWA primary data source for WES review) released their updated chromium VI TWA-TLV® of 0.0002 mg/m^3 (inhalable fraction) in 2017. They also suggest a STEL value of 0.0005 mg/m^3. These were recommended to protect from severe irritation of the upper and lower respiratory tract and from decreases in lung function in exposed workers. They were also expected to minimise respiratory sensitisation and reduce the likelihood of lung cancer, sinonasal cancer and asthmatic responses in sensitised individuals. They cite the NIOSH risk assessment on excess lung cancer deaths as being approximately 1 per 1,000 workers at 0.0002 mg/m^3 for a working lifetime.

SCOEL (2017) concludes that chromium VI compounds are carcinogens with no threshold, hence did not assign a TWA limit value. However, excess risk of lung cancer was calculated using the exposure response relationships from the last updates of two cohort studies. They conclude that excess lung cancers would be approximately 0.4 per 1,000 workers at 0.0001 mg/m^3 for a working lifetime, consistent with the ACGIH estimate.

The SWA recommended TWA-WES for chromium VI of 0.000007 mg/m^3 was calculated at a minimal cancer risk level applying an inhalation unit risk value based on data from a USEPA (SWA secondary data source) study reporting an increased risk of lung cancer in exposed workers. This study was last updated in 1998 and is based on a 1975 conference paper by Mancuso of a proportional mortality study of a cohort of chromate workers from 1931-1937 with exposure data derived from a hygiene study in 1949, where the concentration of chromium in the air of mist and dust was determined by precipitating electrostatically on a bright-line haemocytometer. One might ask why give precedence to a secondary data source over a primary source. Additionally, given that the IRIS unit cancer risk estimate is based on what could only be described as ‘questionable’ grab sample exposure estimates, one has to be somewhat sceptical about the SWA proposed chromium VI WES of 0.000007 mg/m^3.

While the above estimates of excess cancer are based on the assumption of there being no threshold level of effect of occupational chromium VI exposure on lung cancer, Birk et al (2006) derived data that suggested a possible threshold effect. In a mortality study of two German chromate production facilities, which evaluated possible dose-response relationships between hexavalent chromium exposure and lung cancer, lung cancer risk was elevated only in the highest exposure group (SMR = 2.09, 95% CI = 1.08-3.65) on the basis of urinary chromium data.

However, the US Occupational Safety and Health Administration (OSHA, 2006) rejected Birk et al’s conclusion that ’these data suggest a possible threshold effect‘of Cr (VI) exposure on lung cancer. The final OSHA (2006) standard notes that Birk et al study’s small cohort size, few lung cancer cases (e.g. 10 deaths in the three lowest exposure groups combined) and limited follow up (average 17 years), severely limit the power to detect small increases in risk that may be present with low cumulative exposures.

Never the less, de Flora (2000) also conclude that ‘All experimental and epidemiological data, and the underlying mechanisms, point to the occurrence of thresholds in chromium (VI) carcinogenesis.’

Proctor et al (2014) conclude that 'non-linear approaches should be considered for evaluating Cr(VI) lung cancer risk' and that the weight of evidence does not support a mutagenic mode of action for Cr(VI)-induced lung cancer. That is, there are two schools of thought regarding the carcinogenicity of chromium VI – one that believes there is a threshold effect and one that there is no threshold effect. A lower WES will be derived if there is no threshold effect.

OSHA conclude that, based upon the best evidence currently available, at their old permissible exposure limit (PEL) of 0.1 mg/m^3 for Cr (VI), workers would face a significant risk to material impairment of their health. The evidence in the record for this rulemaking indicates that workers exposed to chromium VI are at an increased risk of developing lung cancer, and may also result in asthma and damage to the nasal epithelia and skin. After considerable consultation, the final rule (OSHA Standard Number 1910.1026) establishes an 8-h TWA exposure limit of 0.0005 mg/m^3, with an action level of 0.00025 mg/m^3.

Comment on measurement and analysis

The RQL for chromium VI as stated in the OSHA Sampling and Analytical Method number ID-215 is around 0.000003 mg/m^3. The RQL for chromium VI using NIOSH Analytical Method number 7600, collecting 400 litres of air, is approximately 0.00025 mg/m^3.

The measurement technique should be able to assess exposure at 0.1 times the WES for an 8-hour TWA (European Commission, 2017).

MCA Recommendation

SWA should conduct more review on the carcinogenicity of chromium VI. In the interim, it would probably make sense to adopt the OSHA limit value as a TWA-WES. Of course, quantification of any recommended value using currently available sampling and/or analysis techniques needs to be checked.

In addition, the MCA notes that the WES needs to be practicably implemented in the workplace. Chromium VI exposures in the workplace can be around 0.03 to 0.05 mg/m^3. This is around 4 orders of magnitude higher than the SWA proposed chromium VI WES of 0.000007 mg/m^3. Given that Powered Air Purifying Respirators (PAPRs), correctly worn, have a Required Minimum Protection Factor (RMPF) of 50, meaning that they supply breathing air a minimum 50 times cleaner than the wearer would otherwise be breathing unprotected, and supplied air respirators provide the wearer with a RMPF of 100+, it is unlikely that any respiratory protection will be able to provide adequate protection to meet this WES.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

Birk, T, KA Mundt, LD Dell, RS Luippold, L Miksche, W Steinmann-Steiner-Haldenstaett & D Mundt (2006). Lung Cancer Mortality in the German Chromate Industry, 1958 to 1998. *J Occup Environ Med, 48(4)*: pp 426-433.

De Flora, S (2000). Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. *Carcinogenesis, 21(4)*; pp 533–541 - https://academic.oup.com/carcin/article/21/4/533/2733644.

European Commission (2017). *Methodology for derivation of occupational exposure limits of chemical agents* - The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL), Luxembourg: Scientific Committee on Occupational Exposure Limits – see https://op.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1

OSHA (2006). *Occupational exposure to hexavalent chromium, final rule*. 71 Federal Register 10180. February 28, 2006. 11 Section 6(b) 5, Occupational Safety and Health (OSHA) Act of 1970, Public Law 91-596 - https://www.ncbi.nlm.nih.gov/pubmed/16528853.

Proctor, DM, M Suh, SL Campleman & CM Thompson (2014). Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. *Toxicology, 325*; pp 160-179.

SCOEL (2017). *Recommendation from the Scientific Committee on Occupational Exposure Limits for chromium VI compounds*. SCOEL/REC/386.

15. COAL TAR PITCH VOLATILES (as benzene solubles)

SWA recommends that the TWA-WES for coal tar pitch volatiles (CTPV - as benzene soluble) be reduced from 0.2 mg/m^3 to 0.0001 mg/m^3 (0.1 µg/m^3), to minimise the potential for lung cancers and other tumours in exposed workers.

SWA notes that there is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques.

A number of Western world countries have set an exposure limit for CTPV or polycyclic aromatic hydrocarbons (PAH - as benzene soluble) of between 0.14 and 0.2 mg/m^3, as per the Gestis database for international limit values, with most being set at the latter value.

Comment on toxicological information and data

Under GHS, CTPVs are classified as being a category 1A carcinogen as well as a skin sensitiser. The AIOH (2016b) position paper notes that there is a good relationship between benzo(a)pyrene (B[a]P) and total PAH concentrations in CTPVs, providing a useful tool for assessing exposure to a complex mixture such as PAHs in air. B[a]P is classified by IARC (2012) as a confirmed human carcinogen Category 1, and a number of other PAHs have been classified as Category 2A, i.e. as probably carcinogenic to humans. Studies have shown a statistically significant excess of bladder and lung cancer incidence for men exposed to benzene-soluble material / B[a]P (AIOH, 2016b).

SWA note that the critical effects in humans that are associated with exposure to CTPVs are unclear as separation of the various components is not practicable, hence their assessment of coal tar pitch exposures is based on the identified key solvent components (B[a]P, benzene and others), which based on the mode of action for their carcinogenicity, are characterised as non-threshold based genotoxic carcinogens (ACGIH, 2018; NICNAS, 2015). As such, the SWA proposed WES is based on US EPA (2017) Inhalation Unit Risk for B[a]P to minimise potential for lung cancers and other tumours.

PAH exposure may occur through the three main routes of uptake by the body: inhalation, ingestion and skin absorption (ATSDR, 1995), with air inhalation and skin usually being the two key routes.

The AIOH (2016b) PAH Position Paper suggests a more appropriate approach would be to place the emphasis of exposure on the measurement of the levels of the 16 priority EPA PAHs and specifically B[a]P, and that the CTPV WES should be replaced by a B[a]P 8-h TWA-WES of 0.0002 mg/m^3. Due to skin absorption, AIOH also recommend that biological monitoring of 1-hydroxypyrene be used and exposures interpreted against a biological guidance value of 4.0 µmol/mol creatinine.

Comment on measurement and analysis

NIOSH Analytical Methods[2] 5506 and 5515 are the most often used air sampling methods for PAHs. These methods assume that the PAHs in the particulate collected, measured as the benzene-soluble fraction, are completely desorbed along with other hydrocarbons in the analysis process. This results in some shortcomings in that the true carcinogenic potential may be either over- or under-estimated, depending on the specific PAHs present in the mixture. There is also the additional complication that any other substances that are benzene soluble will also be measured.

The limit of quantitation for method 5506 is said to be 0.0051 µg B[a]P per sample.

MCA Recommendation

Considering the above data, the MCA prefers that the AIOH recommendation be used. Considering the carcinogenic effect, exposures should be controlled to as low as reasonably practicable (ALARP). In addition, medical surveillance is required, including biological monitoring (in urine), to take into

[2] Note that, due to the carcinogenicity of benzene, toluene or cyclohexane are generally used as the extractant for collected samples.

account the potential for skin absorption as well as to check on the efficacy of controls, primarily respiratory protection and for hand-to-mouth contamination.

In fact, given the complex aspects of CTPV / PAH toxicity, rather than depend on a 'one-size-fits-all' regulatory exposure limit (WES), the MCA believes it would be best to have an industry-specific guidance / best practice approach.

SWA also needs to clarify quantification of the recommended value with currently available sampling and analysis techniques available in Australia.

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16. COPPER FUME, DUST AND MIST (as Cu)

SWA recommends that the TWA-WES for copper fume of 0.2 mg/m^3 and for copper dusts and mists of 1 mg/m^3 be each reduced to 0.01 mg/m^3. This revised TWA-WES value is recommended to protect for irritant and adverse lung effects in exposed workers and is consistent with the SCOEL (2014) recommendation.

SWA notes that there is uncertainty regarding quantification of the recommended value with currently available sampling and/or analysis techniques.

Most of the Western world has set an exposure limit for copper fume, dust and metal, as per the Gestis database for international limit values. For copper and inorganic copper compounds, most are set at 0.1 mg/m^3 or higher for the inhalable fraction or 0.01 mg/m^3 for the respirable fraction. For copper dust and mists, most are set at 1 mg/m^3. For copper fume, most are set at 0.1 to 0.2 mg/m^3.

Comment on toxicological information and data

SWA note that the:

> Critical effect associated with inhalation of copper is local irritation of the respiratory tract. Concentrations of metal copper dust in the order of 0.1 mg/m^3 are reported to be associated with a condition similar to metal fume fever.

ACGIH (2018) note that copper fumes are considered the primary exposure consideration in relation to health effects. They note that inhalation exposure to copper has been reported to cause nasal irritation and produce symptoms associated with metal fume fever. However, few health effects have been reported in humans that have been accompanied by exposure assessment. They specify a higher exposure standard for dust and mist (inhalable copper particulate mass), as compared to fume (respirable copper particulate mass).

Current ACGIH documentation notes a copper fume TWA-TLV® of 0.2 mg/m^3 and a dust / mist TWA-TLV® of 1 mg/m^3, the same as the current SWA WES. Based on a human study of inhalation of copper metal dust generated by vibrational resuspension of copper dust originally formed using a polishing wheel (Gleason, 1968 – cited by ACGIH), draft documentation for a notice of intended change by ACGIH® recommended a TWA-TLV® for inhalable particulate of 0.1 mg/m^3. For respirable particulate copper, a TWA-TLV® of 0.05 mg/m^3 was recommended, based on a study of mice. However, the notice of intended change has not been taken up. Copper remains on the 'Under Study' list.

SCOEL (2014) also use the Gleason (1968) reference for determining repeated dose toxicity from human studies. They note that:

> The effects (general feeling of discomfort, slight sensations of chills and warmth, stuffiness of the head) were first reported some weeks after the start of exposure. Measured exposure was 0.12 mg/m^3 but, according to the author, the workers may sometimes have been exposed to 2- to 3-fold higher concentrations. The effects did not disappear until an exhaust system was installed, which reduced exposure to 0.008 mg/m^3.

This appears to be the source of the 0.008 mg/m^3 human NOAEC value quoted by SWA in their documentation. It is well below the measured exposure concentrations. SCOEL (2014) recommend a 0.01 mg/m^3 exposure limit for the respirable fraction of copper, essentially the fume component, noting that it applies to copper and all its inorganic compounds.

Krabbe et al (2019) found a persistent increase of systemic inflammatory markers (c-reactive protein - CRP) indicating an elevated risk for welders chronically exposed to zinc- and copper-containing welding fumes. Brand et al (2019) found that 5-hour exposure of workers to copper- and zinc-containing brazing fumes (2.5 mg/m^3) induced an increase of CRP, whereas shorter exposure times did not result in a significant inflammatory reaction. That is, reducing daily exposure times below 5 hours is able to prevent systemic inflammatory reactions. In a more recent publication by Brand et al

(2020), no observed effect levels of between 0.2 and 0.3 mg/m^3 was found for systemic inflammation in 15 healthy male volunteers exposed to welding fumes containing copper.

Comment on measurement and analysis

Copper in welding fume can range from 0.001 to 0.08 mg/m^3, or up to 0.15 mg/m^3 with an average of 0.032 mg/m^3. In a copper mine, inhalable copper average concentrations can range from 0.036 to 0.066 mg/m^3, with a maximum value of 0.62 mg/m^3.

The RQL for copper as stated in the OSHA Sampling and Analytical Method number 1006 is 0.0003 mg/m^3. For Method number 7029, it is around 0.05 mg/m^3, while for NIOSH Analytical Method number 7303 it is around 0.001 mg/m^3. Given the SWA uncertainty as to measurability at 0.01 mg/m^3, this needs to be further assessed.

The measurement technique should be able to assess exposure at 0.1 times the WES for an 8-hour TWA (European Commission, 2017).

MCA Recommendation

Based on the information provided above, the MCA believes it is preferable that there are separate TWA-WESs for copper fume (respirable fraction) and copper dust and mist (inhalable fraction). Also, given the indication that the primary health effect of concern (flu-like symptoms) can be readily controlled by reducing exposure time, it is thought that limits of 0.1 mg/m^3 (inhalable) and 0.05 mg/m^3 (respirable) may be appropriate TWA-WESs. Of course, quantification of the recommended values using currently available sampling and analysis techniques needs to be checked.

The MCA notes that the International Copper Association and European Copper Institute are conducting further scientific studies on exposure standards for copper. These studies are due to be published Q4 2021, thus the MCA suggests that SWA withhold / delay the adoption of the proposed WES until further data is generated and published.

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17. CYANIDES (as CN, inorganic salts)

SWA recommends that the TWA-WES for cyanides (as CN, inorganic salts) be reduced from 5 mg/m^3 to 1 mg/m^3, with a new Peak limitation value of 5 mg/m^3. The TWA value is set to protect against chronic neurological symptoms and thyroid enlargement in exposed workers, while the peak limitation value is recommended to protect for acute exposure resulting in immediate and severe health effects (death, coma, respiratory failure) in exposed workers. Both the proposed TWA and Peak values are generally consistent with the SCOEL (2010) proposed limit values.

SWA notes that the recommended value is quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Many of the Western world countries have set a TWA exposure limit for cyanides of between 0.5 and 5 mg/m^3, as per the Gestis database for international limit values, with most (56%) being set at 5 mg/m^3. STEL values of between 1 and 20 mg/m^3 are used, with most (31%) being set at 5 mg/m^3, some as ceiling / peak values.

Comment on toxicological information and data

The alkali cyanide salts act via the same mechanism as hydrogen cyanide (HCN) which is by the release of cyanide ion (ACGIH, 2018). HCN is a potent and rapidly-acting asphyxiant which prevents tissue utilisation of oxygen by inhibition of the cellular respiratory enzyme, cytochrome oxidase. Inhalation or ingestion of cyanide may produce reactions within a few seconds and death within minutes, depending upon concentration. The critical effects in humans that are associated with exposure to HCN range from headaches, weakness, dizziness, throat irritation, dyspnoea, thyroid enlargement and an increase in thiocyanate excretion in the urine, to death.

SWA used the LOAEL in humans of 4.7 mg/m^3 as a starting point and applied a factor of five for the lack of a NOAEL (HCOTN, 2012; SCOEL, 2010) to derive a TWA of 1 mg/m^3. Additionally, starting at the LOAEL of 20 mg/m^3 for acute effects and applying a factor of two for slight effects at the LOAEL (HCOTN, 2012) they derived the peak limitation of 5 mg/m^3.

The US EPA (2010) used a LOAEL of 2.5 mg/m^3 HCN, which was based on thyroid enlargement and altered iodide uptake in a cohort of workers in three electroplating facilities who had been exposed to HCN for 5 to 15 years (cited study by El Ghawabi et al, 1975).

The acute exposure effect of HCN in humans is as follows (WHO, 2004):

- 20-40 mg/m^3 - slight effects occur
- 50-60 mg/m^3 - can be tolerated without immediate or late effects for 20 minutes to 1 hour
- 120-150 mg/m^3 - may lead to death after 0.5 to 1 hour
- 150 mg/m^3 - is likely to be fatal within 30 minutes
- 200 mg/m^3 - is likely fatal after 10 minutes
- 300 mg/m^3 is immediately fatal.

Industrial cyanide poisoning is rare in the developed world (presumably because of good work practices) and there are effective cyanide antidotes available, along with indications for their use, the requirements for supportive care and a recommended approach for workplaces where there is a risk of cyanide poisoning (Reade et al, 2012).

MCA Recommendation

Considering the above data, the MCA agrees that the TWA-WES should be changed as suggested, but consider the SCOEL (2010) STEL value of 5 mg/m^3 more appropriate than the proposed peak value.

There is an 'International Cyanide Management Code', which is a voluntary initiative for the gold and silver mining industries and the producers and transporters of the cyanide used in gold and silver mining.

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18. DIESEL ENGINE EMISSIONS

SWA recommends that there be a TWA-WES for diesel engine emissions, but notes that currently there are insufficient data available to recommend a suitable TWA-WES. SWA further notes that emissions:

> From diesel engines consist of a mixture of hundreds of chemical compounds, which are emitted in the gaseous and the particulate phase. The composition of emissions varies depending on several factors including engine type, fuel type and operating conditions. Diesel engine emissions contain carcinogenic substances such polycyclic aromatic hydrocarbons (PAHs) and benzene (DFG, 2014; HCOTN, 2019; SCOEL, 2016).
>
> The evidence strongly suggests that diesel engine emissions, and many of its components, can induce lung cancer in humans through genotoxic mechanisms that include DNA damage (DFG, 2014; HCOTN, 2019; IARC, 2014; SCOEL, 2016). Consequently, diesel engines emissions are characterised as a non-threshold genotoxic carcinogen.

Therefore, given that diesel engine emission (DEE) composition can vary depending on several factors and there are limited data regarding diesel engine emissions from modern engines (post 2007) in the primary sources, SWA suggest that a priority review of additional data sources is recommended at the next scheduled review.

SWA does not discuss the levels of DEE, or diesel particulate matter (DPM), that are readily quantifiable through currently available sampling and analysis techniques.

There are very few countries that have set a TWA exposure limit for DEE/DPM, as per the Gestis database for international limit values. The following values exist:

- Austria – 0.3 mg/m^3 as respirable elemental carbon (REC) aerosol for underground mining and 0.1 mg/m^3 as REC aerosol for the rest (a STEL is also recommended)
- European Union – 0.05 mg/m^3 as REC (applying from 21.02.2023, and for underground mining and tunnelling from 21.02.2026)
- Germany – 0.05 mg/m^3 as REC (not applicable to underground mining until 31 October 2022)
- New Zealand as REC – 0.1 mg/m^3
- Ireland – 0.15 mg/m^3 as respirable fraction (< 0.1 µm)
- Poland – 0.5 mg/m^3 as respirable fraction.

Comment on toxicological information and data

The critical effect in humans that is associated with exposure to DEE/DPM is considered to be lung cancer. The SWA DEE documentation tends to focus on the March 2019 recommendation made by the Health Council of the Netherlands (HCOTN, 2019) in regards to their DPM exposure standard:

> The Committee estimates exposure concentrations of Respirable Elemental Carbon (REC) in the air, a parameter for exposure to diesel engine exhaust powered by petroleum-diesel fuels, which correspond to:
>
> - 4 extra death cases of lung cancer per 100,000 (target risk level), for 40 years of occupational exposure, equals to 0.011 µg /m^3 REC (TWA 8 hour)
> - 4 extra death cases of lung cancer per 1,000 (prohibition risk level), for 40 years of occupational exposure, equals to 1.03 µg/m^3 REC (TWA 8 hour).

The Dutch committee reviewed studies in workers who had been exposed to emissions from diesel engines **with no effective emission reduction systems** to arrive at these target and prohibition risk levels. Their decision is based on risk outcomes from the NCI / NIOSH Diesel Exhaust in Miners Study (DEMS - Silverman et al, 2012) along with the further derived risk assessment by Vermeulen

and Portengen (2016) and meta-analysis of two other previously published and analysed epidemiological studies (Steenland et al 1998, Garshick et al 2012). The risk studies quoted by the Dutch are not new. The Australian Institute of Occupational Hygienists (AIOH, 2017) reviewed the same studies and the published criticisms they attracted in their DPM Position Paper and conclude:

> There are differences of opinion and interpretation regarding the degree of potential for cancer effects of DPM, with most contention on derivation of past exposures.

The Dutch note that three of four studies showed statistically significant positive associations and trends between cumulative REC exposure and lung cancer mortality in the trucking and mining industry, in which workers were mainly exposed to DEE (Steenland et al. 1998, Garshick et al. 2012, Silverman et al. 2012). However, no association was found by Möhner et al. (2013), and this study was considered by the Dutch committee to be 'less suitable for quantitative risk assessment'. They do note the uncertainties associated with the epidemiology studies used that may have influenced the outcome, regarding actual historical exposure levels, smoking or co-exposure to known carcinogenic substances from other sources than diesel engines. They further point out that as yet, there is insufficient scientific data to quantify the efficacy of the latest emission reduction systems, in terms of mitigating or eliminating the risk of cancer or of other adverse health effects incurred by long-term occupational exposure to DEE.

Setting an Occupational Exposure Limit for Diesel Engine Exhaust in Canada: Challenges and Opportunities (CAREX Canada, 2019)[3] (not cited by SWA) highlights the variability in OELs that have been adopted in Canada for constituents of DEE. The report found that few jurisdictions in Canada outside of the mining industry have an OEL for DEE, and none have adopted an OEL that reflects the current state of knowledge. The purpose of the report was to: understand the regulatory landscape for occupational DEE exposure; learn what experts thought are the key barriers and facilitators to setting and complying with OELs; and make a recommendation on a DEE OEL for Canada.

The report notes that elemental carbon (EC) is the best surrogate for measuring diesel exhaust particulate (consistent with the AIOH 2017 opinion) and that several international jurisdictions have proposed or adopted OELs based on measurement of EC. It cites the legally enforceable OELs and also non-legal recommendations for OELs from four professional organisations for DEE (California Department of Public Health, Finnish Institute of Occupational Health, the Health Council of the Netherlands, and the AIOH). They further note that the American Conference of Governmental Industrial Hygienists (ACGIH®) has placed DEE on its list of agents under study but does not currently recommend a TLV for DEE.

Key informants to the CAREX Canada (2019) report identified five key challenges and barriers to the development and implementation of a DEE OEL: uncertainty in the science, slow regulatory processes, economic impact, inconsistencies in the selected marker of exposure, and measurement and analytical issues. Other barriers identified were in relation to the OHS landscape in Canada and the fact that provincial reliance on the ACGIH® (2018) threshold limit values means that jurisdictions will wait until the ACGIH® issues a recommended limit for DEE.

While noting that other jurisdiction current DEE OELs vary between 50 to 100 µg/m^3, based on evidence of increased lung cancer risk at very low levels, CAREX Canada recommend that Canadian jurisdictions move towards an OEL based on elemental carbon of 20 µg/m^3 for the mining industry and 5 µg/m^3 for other workplaces to protect worker health. The higher OEL recommended for the mining industry was said to take into account:

> The feasibility of implementation in this industry that will have particular challenges and is meant as a interim target in a staged approach to eventually have one harmonized OEL for all workers.

In coming to this conclusion, CAREX Canada placed emphasis on the health-based recommendations released by the Health Council of the Netherlands (HCOTN, 2019), considered to

[3] CARcinogen EXposure Canada is a multi-institution team of researchers and specialists with expertise in epidemiology, risk assessment, toxicology, geographic information systems, and knowledge mobilisation.

be particularly noteworthy, 'as they reflect the current state of the evidence and are two orders of magnitude lower than other existing OELs for DEE.'

CAREX Canada interviewees identified the following six key facilitators that they perceive are necessary (or highly desirable) for the implementation of a DEE OEL in their jurisdiction: proof of achievability, strong scientific rationale, a national working group, availability of up-to-date measurement techniques and data, and a consensus recommendation.

SWA notes that:

> In the absence of any more definitive data, the AIOH supports the maintenance of DPM levels (measured as submicron elemental carbon) as low as reasonably practicable (ALARP) below an 8-hour TWA guidance exposure value of 0.1 mg/m^3, with the provision of applying a TWA value of 0.05 mg/m^3 as an action level which triggers investigation of the sources of exposure and implementation of suitable control strategies. The AIOH is of this opinion, as such a limit is a balance between the factors of minimising irritation and minimising the potential for risk of lung cancer to a level that is not detectable in a practical sense in the work force.

Also noted in the AIOH DPM Position Paper, the most modern diesel engine assessed in the epidemiology studies previously mentioned, was built in 1983, whilst the exhaust produced by new technology diesel engines is totally different to that from old engines.

Comment on measurement and analysis

The limit of detection (LOD) of NIOSH Analytical Method number 5040 for DPM (as elemental carbon) is around 2 µg/m^3, with studies in Australian coal mines being at around 1 µg/m^3 (Rogers, 2005). The level of quantitation will be higher.

When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission (2017) state that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA'.

It is also worth noting that background environmental levels of DEE/DPM are around 1-2 µg/m^3.

MCA Recommendation

Considering the above data, the MCA agrees that further study is required to determine an appropriate TWA-WES for DEE/DPM, taking into account measurability. Such a WES certainly must be measurable and discernible from DEE/DPM background environmental levels. In the interim, the AIOH (2017) recommendations for DPM could be used: as low as reasonably practicable below an 8-hour TWA guidance exposure value of 0.1 mg/m^3 (measured as submicron EC), with the provision of applying a TWA value of 0.05 mg/m^3 as an action level.

Note that NSW mines have introduced a DPM exposure standard of 0.1 mg/m^3 EC, commencing 1 February 2020 with phase in for 12 months and referencing it against AIOH DPM Position Paper value.

Given the complex aspects of DEE/DPM toxicity, rather than depend on a 'one-size-fits-all' regulatory exposure limit (WES), the MCA believes it would be best to have an industry-specific guidance / best practice approach. Such approaches already exist, as follows:

- Mine Safety Operations Division of the New South Wales Department of Primary Industries publications MDG29 Management of diesel engine pollutants and MDG 43 Technical Standard for the design of diesel engine systems for use in underground coal mines
- Western Australia Department of Mines, Industry Regulation and Safety publications Guideline - Management of diesel emissions in Western Australian mining operations and Guideline - Purchase, operation and maintenance of underground diesel engined mining equipment

- Queensland Department of Natural Resources, Mines and Energy publication Diesel Emissions Management in Underground Coal Mines - Best Practices and Recommendations
- Australian Institute of Occupational Hygienists (AIOH) publication A Guideline for the Evaluation & Control of Diesel Particulate in the Occupational Environment
- Safe Work Australia publication Guidance for managing the risks of diesel exhaust.

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19. FLUORIDES (as F)

SWA recommends that the TWA-WES for fluorides (as F) be retained at 2.5 mg/m^3 as an interim value, to protect against irritation of the eyes and respiratory tract and minimise the potential for fluorosis in exposed workers. Given the data available from SWA primary sources, SWA recommends that a review of additional sources be conducted at the next scheduled review. The current TWA value is consistent with the TLV® recommended by the ACGIH (2018).

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Much of the Western world has set a TWA exposure limit for fluorides (as F) of between 1 and 2.5 mg/m^3, as per the Gestis database for international limit values, with most (75%) being set at 2.5 mg/m^3. STEL values are much fewer (only 5 countries), varying between 2 and 5 mg/m^3, with most (60%) being set at 4 mg/m^3.

Comment on toxicological information and data

Most epidemiological studies have investigated whether there is a connection between the fluoride concentration in drinking water and adverse effects on health, particularly with skeletal effects and cancer. Most of the studies quoted are population-based and provide no data concerning individual exposure or any particular fluoride compound (ATSDR, 2003). In addition, ATSDR (2003) note that most of the available literature on fluoride toxicity concerns sodium fluoride. Additional toxicity literature is available on some other forms of fluoride, such as stannous fluoride. Further, they note the primary exposure route and duration for fluoride as being chronic oral exposure to fluoride in the drinking water, food and fluoride-containing dental products. The major health effect of chronic inhalation exposure to fluoride, as for other routes of uptake, is skeletal fluorosis, manifested as an accumulation of fluoride in the bones with resultant brittleness.

According to SWA, the critical effects in humans that are associated with exposure to fluorides are irritation of the eyes and respiratory tract and bone changes due to skeletal fluorosis. Complaints of eye and respiratory passage irritation and nausea associated with concentrations of 5 mg/m^3 have been reported. Nosebleeds are reported following exposure to fumes containing greater than 10 mg/m^3, but there are no effects at below 2.5 mg/m^3. No bone changes were identified in a group of workers exposed to fluoride averaging 2.65 mg/m^3 (ACGIH, 2018).

DFG (2006) note that skeletal fluorosis is the most sensitive parameter for the systemic effects of exposure to fluorides. Citing studies by Derryberry et al (1963) and Kaltreider et al (1972), DFG (2006) note that fluoride concentrations in air of more than 2.4 to 6 mg/m^3 or 3.4 mg/m^3 resulted in skeletal fluorosis in workers exposed for 10 years and more, whereas no effects on the skeleton were found in workers exposed for 10 years to average fluoride concentrations of 2.4 or 2.65 mg/m^3.

SCOEL (1998) recommend an exposure limit of 2.5 mg/m^3 for mixtures of inorganic fluorides and hydrogen fluoride. They report that skeletal fluorosis was not found in aluminium workers whose urine was monitored, average concentrations being 2.78 mg F^-/L in pre-shift samples and 7.7 mg F^-/L in post-shift samples for the high-exposure group (Dinman et al, 1976). An end of shift value of 8 mg F^-/L was indicated as being equivalent to an average exposure of 2.5 mg/m^3. ATSDR (2006) also note the Dinman et al study.

ACGIH (2018), in their documentation for a urinary fluoride BEI, note that due to confounding from background levels (~ 1 mg/L) and the continuum between exposure and effect, no definite associations between certain urinary fluoride levels and particular phases of skeletal fluorosis can be observed.

Romundstad et al (2000) found an association between exposure to potroom emissions measured by fluorides and mortality from asthma, emphysema and chronic bronchitis combined, in the Norwegian primary aluminium industry. However, Radon et al (1999) determined that lung function impairment in

the modern primary aluminium industry may be only partly due to fluoride exposure. Donoghue et al (2011) examined the incidence of occupational asthma for seven aluminium smelters in Australia/New Zealand from 1991 to 2006. They conclude that controlling exposures to below the current exposure limits and undertaking pre-placement medical assessments seem to have contributed to a substantial decline in occupational asthma incidence.

DFG (2006) go on to state that their previous exposure limit value of 2.5 mg/m^3 (equivalent to 20 years of exposure to doses of 25 mg per day) is possibly not sufficient protection against effects on the bones. Citing the US EPA (1985) recommendation of an upper limit total fluoride intake of 10 mg per day, DFG state that this dose is equivalent to a TWA airborne concentration of 1 mg/m^3, assuming inhaling 10 m^3. They also note that their recommended exposure limit of 1 mg/m^3 finds support from a Chinese study indicating that the intake of 14 mg fluoride per day (fluoride doses of about 0.25 mg/kg body weight; corresponding to 1.5 mg/m^3 assuming body weight to be 70 kg and the volume of air inhaled in 8 hours to be 10 m^3) over 20 years results in a greater number of bone fractures, which was not found at doses of 7.85 mg and day (about 0.15 mg/kg body weight; corresponding to 1 mg/m^3 with a body weight of 70 kg and 10 m^3 air inhaled in 8 hours).

Australia and New Zealand use an upper nutritional limit (that won't exceed intakes that are associated with severe dental fluorosis) of 10 mg per day (NHMRC, 2017). This NOAEL of 10 mg per day was derived based on the relationship between fluoride intake and skeletal fluorosis, from published studies from 1954 to 1997.

EFCA (2006) note that numerous epidemiological data support a linear relationship between fluoride intake and bone fluoride content and between bone fluoride content and both incidence and severity of skeletal fluorosis. In the few cases of clinical skeletal fluorosis in which the fluoride intake could be estimated, it ranged from 15 to 20 mg per day and the period of exposure was over 20 years. 'A more precise threshold dose for fluoride causing skeletal fluorosis cannot be defined.'

MCA Recommendation

Considering the above data, the MCA agrees that further study on an appropriate TWA-WES for fluorides is required, but agree with retaining the current 2.5 mg/m^3 limit value. It best reflects workplace exposure observations on airborne concentrations of fluorides that do not cause fluorosis. The MCA believes that the use of total body intake of fluoride per day to derive a workplace airborne contaminant limit, as used by DFG (2006), is tenuous.

The MCA questions the need for a regulatory exposure limit (WES) for irritation. Any change to the WES should take into consideration current toxicological data as well as the severity of associated health outcomes.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

ATSDR (2003). *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine*. Agency for Toxic Substances & Disease Registry (ATSDR) – see https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=212&tid=38

Deutsche Forschungsgemeinschaft (DFG) (2006). *Fluorides – MAK value documentation* – see https://www.onlinelibrary.wiley.com/doi/book/10.1002/3527600418.

Donoghue, MD, N Frisch, M Ison, G Walpole, R Capil, C Curl, R Di Corleto, B Hanna, R Robson & D Viljoen (2011). Occupational asthma in the aluminum smelters of Australia and New Zealand: 1991–2006. *Am J Ind Med 54(3)*; pp 224-231.

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NHMRC (2017). *Nutrient Reference Values for Australia and New Zealand – Fluoride*. National Health and Medical Research Council (NHMRC) – see https://www.nrv.gov.au/nutrients/fluoride.

Radon, K, D Nowak, R Heinrich-Ramm & D Szadkowski (1999). Respiratory health and fluoride exposure in different parts of the modern primary aluminum industry. *Int Arch Occup Environ Health 72(5)*; 297-303.

Romundstad, P, A Andersen & T Haldorsen (2000). Nonmalignant mortality among workers in six Norwegian aluminum plants. *Scand J Work Environ Health, 26(6)*; pp 470-475.

SCOEL (1998). *Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for Fluorine, Hydrogen Fluoride and Inorganic Fluorides (not uranium hexafluoride)*. SCOEL/SUM/56.

20. HEXANE (n-HEXANE)

SWA recommends that the TWA-WES for n-hexane be increased from 20 ppm to 50 ppm, to protect against neurotoxic effects in exposed workers. The proposed TWA value is consistent with the TLV® recommended by the ACGIH (2018).

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Much of the Western world has set a TWA exposure limit for n-hexane of between 20 and 500 ppm, as per the Gestis database for international limit values, with most (54%) being set at 20 ppm, although 36 percent are set at 50 ppm. STEL values are much fewer (only 6 countries), varying between 50 and 400 ppm, with most (50%) being set at 400 ppm.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to n-hexane are neurotoxicity including polyneuropathy and narcosis. Numerous case reports exist reporting polyneuropathy in workers following exposure to solvents containing n-hexane (ACGIH, 2018; DFG, 2000).

SWA notes that the original TWA-TLV® of 25 ppm for n-hexane was based on studies involving exposures to solvent assumed to contain 30 percent n-hexane, which upon detailed review of that data identified n-hexane content at 50 to 70 percent, hence the change up to 50 ppm.

The ACGIH TWA-TLV® of 50 ppm was based primarily on studies showing peripheral neuropathies at exposure levels as low as 210 ppm (Miyagaki, 1967; Inoue et al, 1970). NIOSH (1989) based its 100 ppm REL on the same studies as those cited by the ACGIH. NIOSH reasoned that:

> The absence of definitive epidemiologic or toxicologic evidence makes it difficult to determine how much lower the environmental limit should be. Professional judgment suggests [that] a TWA concentration of 350 mg/m^3 (100 ppm) offers a sufficient margin of safety to protect against the development of chronic nerve disorders in workers.

OSHA decided then to adopt a 50 ppm exposure limit.

DFG (2000) recommend a TWA exposure limit of 50 ppm, based on both human and animal studies.

MCA Recommendation

Considering the above data, the MCA agrees with increasing the current TWA-WES to 50 ppm.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

Deutsche Forschungsgemeinschaft (DFG) (2000). *N-Hexane – MAK value documentation* – see https://www.onlinelibrary.wiley.com/doi/book/10.1002/3527600418.

NIOSH (1989). *n-Hexane* - OSHA comments from the January 19, 1989 Final Rule on Air Contaminants Project – see https://www.cdc.gov/niosh/pel88/110-54.html.

21. HYDROGEN CYANIDE

SWA recommends that the Peak limitation WES for hydrogen cyanide (HCN) be reduced from 10 ppm (11 mg/m^3) to 4.7 ppm (5 mg/m^3), to protect against immediate and severe health effects (death, coma, respiratory failure) in workers exposed at the workplace. SWA also includes a TWA-WES of 0.9 ppm (1 mg/m^3), to protect against chronic neurological symptoms and thyroid enlargement in exposed workers. Both the proposed TWA and Peak values are generally consistent with the SCOEL (2010) proposed limit values. In fact, the documentation and proposed exposure limits are consistent with that for cyanides (as CN, inorganic salts), as previously commented on.

SWA does not discuss the levels of hydrogen cyanide that are readily quantifiable through currently available sampling and analysis techniques, but does so for cyanides (as CN, inorganic salts).

Some countries in the Western world have set a TWA exposure limit for hydrogen cyanide of between 0.27 and 10 ppm, as per the Gestis database for international limit values, with most (46%) being set at 0.9 ppm. STEL (or Ceiling – 25%) values of between 0.9 and 10 ppm are used by more countries, with most (60%) being set at 4.5/4.7 ppm.

Comment on toxicological information and data

SWA notes that hydrogen cyanide and cyanide salts have very similar toxicological endpoints and effects acting primarily through the release of the cyanide ion (ACGIH, 2018). The critical effects in humans that are associated with exposure to hydrogen cyanide are thus the same as discussed for cyanides (as CN, inorganic salts).

MCA Recommendation

Consistent with MCA comments for cyanides (as CN, inorganic salts), the MCA agrees that the TWA-WES should be changed as suggested, but considers the SCOEL (2010) STEL value of 5 mg/m^3 more appropriate than the proposed peak value.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

SCOEL (2010). *Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for cyanide (HCN, KCN, NaCN)*. SCOEL/SUM/115.

22. HYDROGEN FLUORIDE (as F)

SWA recommends that the Peak limitation WES for hydrogen fluoride (HF) be reduced from 3 ppm to 2 ppm, to protect against acute respiratory tract damage in exposed workers. SWA also includes a TWA-WES of 0.5 ppm, to protect against eye, skin and respiratory tract irritation and to reduce the risk of skeletal fluorosis in exposed workers. Both the proposed TWA and Peak values are consistent with the TLVs® recommended by the ACGIH (2018).

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.' Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA are uncertain.

Much of the Western world has set a TWA exposure limit for hydrogen fluoride (as F) of between 0.5 and 3 ppm, as per the Gestis database for international limit values, with most (56%) being set at 1.8 ppm. STEL (or Ceiling – 24%) values of between 2 and 6 ppm are used, with most (67%) being set at 3 ppm, although 24 percent are set at 2 ppm.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to HF are irritation of the respiratory system, eyes and skin and skeletal fluorosis. HF is also corrosive, hence the Peak limitation value.

A number of studies have examined the acute toxicity of HF in humans under accidental exposure conditions or experimental conditions and in laboratory animals (ATSDR, 2003). These studies demonstrate that the respiratory tract is the most sensitive target of toxicity. At slightly higher concentrations, skin and eye irritation are also observed.

SWA states that the ACGIH derived their TLV-TWA of 0.5 ppm (0.4 mg/m^3):

> Based on a NOAEC of 0.9 ppm …. Given the evidence of irritation at concentrations greater than 3 ppm and the outcome, it is likely that ACGIH divided the NOAEC by a factor of two to derive their TLV-TWA.

The ACGIH (2018) documentation actually states that their TLV-TWA of 0.5 ppm was based on 'the results of controlled inhalation studies in healthy human volunteers, which showed symptom increases and bronchoalveolar lavage fluid changes in the 0.6 to 2.4 mg/m^3 group (0.9 to 2.9 ppm).' This is based on work published by Lund et al (1997 & 1999), in which a 1-hour exposure to HF concentrations was used to observe symptoms of irritation, respiratory function and the potential for inflammatory reaction in the airways.

Lund et al (1997) exposed 20 healthy male volunteers for 1 hour to constant HF concentrations ranging from 0.2 to 5.2 mg/m^3. The total symptom score was significantly increased at the end of exposure for all the subjects as a group ($P < 0.01$) and for the group exposed to HF below 0.6 mg/m^3 (0.9 ppm). No change was detected in FEV_{15} although a significant decrease was found in forced vital capacity (FVC) in the group exposed to fluorides below 0.9 ppm and for the entire group. Almost all the symptoms had disappeared four hours after the end of exposure. Symptom scores from the upper airways were significantly correlated with the HF concentration, the change in plasma fluoride concentration and the maximum plasma fluoride concentration. A significant correlation was also found between the total symptom score for airways and the HF concentration. ACGIH (2018) note however that the post-exposure decrease in FVC for the low exposure group (0.24-0.73 ppm) was not observed in the higher dose exposure groups, hence the lung function decrements were not dose related. They also note the same conclusion for upper airways and eye symptoms, where the low- and high-dose groups had increased scores, but the mid-dose group did not.

Lund et al (1999) exposed 19 healthy non-smoking male volunteers for 1 hour to constant low (<0.6 mg/m^3), intermediate (0.7-2.4 mg/m^3), or high (2.5-5.2 mg/m^3) concentrations of HF. There was a significant increase in the percentage of CD3 positive cells in the bronchial portion for those exposed to 'intermediate' and 'high' concentrations. For the 'high' exposure group the increase in the bronchoalveolar portion was also significant. A significant correlation was found between the increase in the percentage of lymphocytes and CD3 positive cells in the bronchoalveolar portion. Myeloperoxidase and interleukin-6 increased significantly in the bronchial portion for those exposed to 'high' concentrations. These results indicated that such HF concentrations 'may induce an inflammatory reaction in the airways.'

The epidemiology studies reviewed by ACGIH (2018) indicate no significant changes in pulmonary function due to occupational exposure to an average of 1.03 ppm HF, no increase in worker respiratory complaints for HF concentrations less than 3 ppm (2.5 mg/m^3), and a threshold for minimal increase in fluorosis (Grade I) being below 4.3 ppm (3.38 mg/m^3).

The ACGIH (2018) mention the controlled human exposure studies published by Largent and Columbus (1960), but place little emphasis on them. The SCOEL (1998) documentation notes that exposure of 5 volunteers to HF at concentrations in the region of 2.6 to 4.7 ppm (2.1-3.9 mg/m^3) for 6 hours per day over 10 to 50 days, gave rise to slight irritation of the facial skin, eyes and nose (Largent & Columbus, 1960). Exposures to an average concentration of 1.42 ppm (1.2 mg/m^3) were considered to have no effects, although an unpleasant taste in the mouth was experienced.

SCOEL (1998) recommends a TWA of 1.5 mg/m^3 and a STEL of 3 ppm. They note that the STEL value was proposed for HF to limit peaks in exposure which could result in irritation, based on the study by Largent and Columbus (1960).

ATSDR (2003) note that single exposures to relatively low concentrations of HF (≥0.5 ppm) can result in upper respiratory tract irritation in humans. The odour threshold for HF is around 0.04 ppm (ACGIH, 2018).

Comment on measurement and analysis

The LOD for hydrogen fluoride as stated in NIOSH Analytical Method number 3800 is 0.93 ppm, and for Method number 7906 it is around 0.16 ppm (Breuer & Ashley, 2014). For NIOSH Analytical Method number 7902 it is around 0.07 ppm. For OSHA Sampling and Analytical Method number ID-110, the LOD is around 0.05 ppm. The level of quantitation will be higher.

When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission (2017) state that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA.'

MCA Recommendation

Considering the above data, the MCA believes that a HF TWA-WES of 1 ppm and a STEL of 3 ppm would be sufficiently protective of health and irritation for the majority of workers. The MCA questions the need for a regulatory exposure limit (WES) for a substance where irritation is the primary health effect and the substance has warning properties. Any change to the WES should take into consideration current toxicological data as well as the severity of associated health outcomes.

SWA also needs to clarify quantification of their recommended values with currently available sampling and analysis techniques in Australia.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

ATSDR (2003). *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine*. Agency for Toxic Substances & Disease Registry (ATSDR) – see https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=212&tid=38

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Largent, EJ & A Columbus (1960). The Metabolism of Fluorides in Man. *Arch Ind. Health, 21*; pp 328-323.

Lund K, J Ekstrand, J Boe, P Søstrand & J Kongerud (1997). Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. *Occup Environ Med, 54(1)*; pp 32-7.

Lund K, M Refsnes, T Sandstrom, P Sostrand, P Schwarze, J Boe & J Kongerud (1999). Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. *Scand J Work Environ Health, 25(4)*; pp.326-334.

SCOEL (1998). *Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for Fluorine, Hydrogen Fluoride and Inorganic Fluorides (not uranium hexafluoride)*. SCOEL/SUM/56.

23. HYDROGEN SULFIDE

SWA recommends that the TWA-WES for hydrogen sulfide (H_2S) be reduced from 10 ppm to 1 ppm, to protect against irritation effects and central nervous system (CNS) impairment in exposed workers. The previous STEL of 15 ppm has been reduced to 5 ppm, to protect against acute irritation effects and CNS impairment in exposed workers. Both the proposed TWA and STEL values are consistent with the TLVs® recommended by the ACGIH (2018).

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.' Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA are uncertain.

Much of the Western world has set a TWA exposure limit for hydrogen sulfide of between 1 and 10 ppm, as per the Gestis database for international limit values, with most (67%) being set at 5 ppm. STEL values of between 5 and 20 ppm are used, with most (62%) being set at 10 ppm.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to hydrogen sulfide are irritation of the eyes and upper respiratory tract at low concentrations and 'knockdown effect' at high concentrations. The odour threshold ranges from approximately 0.0002 to 0.3 ppm (ACGIH, 2018). Storage of hydrogen sulfide in the human body is limited by rapid metabolism and excretion (WHO, 2003).

The ACGIH (2018) state that both their TLV-TWA and TLV-STEL values are derived from human and animal data that showed similar qualitative and quantitative responses following single and repeated exposures. Both the TWA and STEL values were based on human data that indicated the start of the dose-response curve for short-term human exposure was around 5 ppm.

Nasal olfactory lesions were reported in Sprague-Dawley CD rats exposed to hydrogen sulfide for 6 h/d and 7 d/wk for 10 weeks at 30 or 80 ppm; the no-observed-adverse-effect level (NOAEL) was 10 ppm (Brenneman et al, 2000). This NOAEL is used as a basis for the development of a medium-term tolerable concentration (WHO, 2003).

SWA notes that the same study showing a NOAEL 'of 10 ppm for nasal lesions, as identified in rats and mice exposed for six hours per day for up to 90 days', is used by each of the primary sources to assign different exposure standard recommendations. These range from a TWA-WES of 1 ppm (ACGIH, 2018) to 10 ppm (HCOTN, 2006). SCOEL (2007) proposed a TWA limit value of 5 ppm by applying an 'uncertainty' factor of 2 to the NOAEL of 10 ppm.

In a human volunteer study, no adverse cardiovascular effects were seen in healthy individuals exposed to 5 or 10 ppm hydrogen sulfide during 30 minutes of submaximal exercise, nor were any changes seen in pulmonary function tests in a separate study when healthy volunteers were exposed to 10 ppm for 15 minutes. However, asthmatics were potentially more sensitive, with 2 out of 10 showing evidence of bronchoconstriction and 3 complaining of headache after exposure to 2 ppm hydrogen sulfide (WHO, 2003).

At higher concentrations hydrogen sulfide inhibits critical respiratory enzymes, leading to paralysis of the respiratory centre and rapid death by asphyxiation; this can occur at concentrations as low as 1,000 to 2,000 ppm (ACGIH, 2018).

The inhalation health effects following exposure to hydrogen sulfide is summarised as follows (adapted from ACGIH, 2018; US Chemical Safety and Hazard Investigation Board, 2014; WHO, 2003):

- 0.05 ppm (0.0002-0.3 ppm): Rotten egg odour detectable by most humans. Odour threshold is highly variable
- 1 – 5 ppm: Moderately offensive odour, possibly with nausea, or headaches with prolonged exposure. Bronchial constriction may occur in asthmatic individuals
- 5 – 10 ppm: Increased eye complaints due to irritation. Relatively minor metabolic changes in exercising individuals during short-term exposures
- 20 – 50 ppm: Eye, nose, throat and lung irritation, digestive upset and loss of appetite. Can cause dizziness, headache and nausea. Brief exposure to higher concentrations (> 50 ppm) deadens the odour detecting nerves in the nose
- 50 – 100 ppm: Temporary loss of smell and marked dryness and irritation of nose and throat. Prolonged exposure (for several hours or days) to concentrations as low this can cause a runny nose, cough, hoarseness, headache, nausea and shortness of breath
- 100 – 200 ppm: Severe nose, throat and lung irritation, ability to smell odour completely disappears. 100 ppm is the Immediately Dangerous to Life and Health (IDLH) concentration
- 200 – 500 ppm: Excitement, severe headache and dizziness, staggering, unconsciousness, and respiratory failure likely in 5 minutes to 1 hour; possible death in 30 minutes to 4 hours. Potentially fatal build-up of fluid in the lungs (pulmonary oedema) in the absence of central nervous system effects (headache, nausea, dizziness), especially if exposure is prolonged. Note: the symptoms of pulmonary oedema, such as chest pain and shortness of breath, can be delayed for up to 48 hours after exposure
- 500 ppm: Severe lung irritation, excitement, headache, dizziness, staggering, sudden collapse ('knockdown'), unconsciousness and death within 4-8 hours, loss of memory for period of exposure
- 500 – 1000 ppm: Rapid onset of severe toxicity: respiratory paralysis, irregular heartbeat, collapse and death. The higher the concentration, the faster the action of asphyxiation and respiratory paralysis. May be immediately fatal after one or more breaths at > 800 ppm, resulting in an instant unconsciousness or 'knock-down' effect. If not fatal, may cause long-term effects such as memory loss, paralysis of facial muscles, or nerve tissue damage.

Although easily detectable by smell at low concentrations, prolonged exposure to non-lethal concentrations (100-200 ppm) can lead to olfactory fatigue whereby higher and potentially lethal concentrations cannot be perceived.

Comment on measurement and analysis

The LOD for hydrogen sulfide as stated in OSHA Sampling and Analytical Method number 1008 is calculated as being 0.448 ppm for a TWA sample or 1.07 ppm for a peak sample. For this method, the RQL is calculated as being 0.52 ppm for a TWA sample or 1.25 ppm for a peak sample. For OSHA method ID-141, the LOD is 0.4 ppm and the LOQ is 0.9 ppm.

Current hand-held detection equipment for hydrogen sulfide generally has a detection limit of 1 ppm, although some have a lower detection limit (sensitivity) of 0.4 ppm, with 0.1 ppm resolution (smallest detectable change) (Dräger, 2013).

When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission (2017) state that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA.'

MCA Recommendation

Considering the above data, the MCA believes that a hydrogen sulfide TWA-WES of between 1 to 5 ppm and a STEL of between 5 to 10 ppm would be sufficiently protective of health and irritation for the majority of workers, depending upon measurability.

SWA needs to clarify quantification of their recommended values with currently available sampling and analysis techniques in Australia.

References

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

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European Commission (2017). *Methodology for derivation of occupational exposure limits of chemical agents* - The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL), Luxembourg: Scientific Committee on Occupational Exposure Limits – see https://op.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1

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SCOEL (2007). *Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for hydrogen sulphide*. SCOEL/SUM/124.

US Chemical Safety and Hazard Investigation Board (2004). *Safety Bulletin: Sodium Hydrosulfide: Preventing Harm*. No. 2003-03-B; Reprinted November 2004 – see https://www.csb.gov/file.aspx?DocumentId=5643

WHO (2003). *Hydrogen Sulfide: Human Health Aspects*. Concise International Chemical Assessment Document 53 – see http://www.inchem.org/documents/cicads/cicads/cicad53.htm.

24. IRON OXIDE FUME AND DUST (as Fe)

SWA recommends that the TWA-WES for iron oxide fume and dust (Fe_2O_3) be retained as an interim value at 5 mg/m^3 (as Fe, respirable particulate fraction), to protect against lung inflammation and pulmonary siderosis in exposed workers. The proposed TWA value is consistent with the TLV® recommended by the ACGIH (2018).

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Much of the Western world has set a TWA exposure limit for iron oxide fume and/or dust of between 3 and 10 mg/m^3, as per the Gestis database for international limit values, with most (68%) being set at 5 mg/m^3. STEL values are much fewer (only 6 countries), varying between 7 and 10 mg/m^3, with most being set at 10 mg/m^3.

Comment on toxicological information and data

The critical effects in humans that are associated with exposure to iron oxide fume and dust are inflammatory responses in the lungs and pulmonary siderosis. Findings of the available epidemiological data are frequently confounded by mixed exposures to silica, diesel exhaust, radioactive materials in mining-related exposures or other metals in studies of welding fume exposures (ACGIH, 2018). SWA recommends that a prioritised review of the available carcinogenicity data, and therefore the suitability of the interim TWA-WES, be undertaken.

The toxicology and epidemiology data for iron oxides has been reviewed generically and previously by authoritative bodies and independent academics, none of whom found convincing evidence for an association between iron oxide exposure and risk of cancer, specifically lung cancer (Pease et al, 2016). However, the DFG (2011) report on the health effects of iron oxides, which did not consider recent epidemiological data from studies in iron and steel industry workers, classified bioavailable iron oxides as suspected carcinogenic substances. This classification was based primarily on observations in the rat together with considerations of putative mechanisms of tumorigenicity via free bioavailable iron leading to reactive oxygen species formation.

Pauluhn (2011) exposed Wistar rats (nose only) to pigment-sized iron oxide dust (Fe_3O_4, magnetite) in a subchronic 13-week inhalation study according to the OECD testing guidelines. Kinetic analyses made during this post exposure period demonstrated that a diminution in particle clearance and lung inflammation occurred at cumulative exposure levels exceeding the lung overload threshold. The empirical NOAEL and the lower bound 95 percent confidence limit on the benchmark concentration obtained by benchmark analysis was 4.7 and 4.4 mg/m^3, respectively, which was said to support a TWA OEL of 2 mg/m^3 (respirable fraction).

Pease et al (2016) note that the rat is known to be more susceptible than other species to the effects of poorly soluble particle lung overload, hence this mode of action is not relevant to human exposure. They further note that there are emerging differences seen in vitro, in cell uptake and cell bioavailability between ‘bulk’ iron oxides (those where greater than 70% of particles are >100 nm in diameter) and ‘nano’ iron oxides (particulates where majority (usually >95%) of pure engineered forms fall in the range 1−100 nm in diameter). From the weight of scientific evidence, ‘bulk’ iron oxides are not genotoxic/mutagenic. Recent evidence for ‘nano’ iron oxide is conflicting regarding genotoxic potential, albeit genotoxicity was not observed in an in vivo acute oral dose study, and ‘nano’ iron oxides are considered safe and are being investigated for biomedical uses; there is no specific in vivo genotoxicity study on ‘nano’ iron oxides via inhalation.

The potential for reactive oxygen species generation as a basis for explaining rodent tumorigenicity is only apparent if free iron from intracellular ‘nano’ scale iron oxide becomes bioavailable at significant levels inside the cell. This would not be expected from ‘bulk’ iron oxide particulates. Pease et al (2016) conclude that based upon the complete weight of evidence, ‘bulk’ iron oxides are not human carcinogens.

Bourgkard et al (2009) studied the possible association between iron oxide exposures and lung cancer risk among workers in a French carbon steel-producing factory. This study did not detect any relationship between exposure to iron oxides and lung cancer mortality. No lung cancer excess was observed for exposure to iron oxides (RR 0.80, 95% CI 0.55 to 1.17) and no dose-response relationship with intensity, duration of exposure or cumulative index was found.

Lewinski et al (2013) provided an overview of the inhalation studies that have been conducted in humans on iron oxides. Both occupational exposure studies on complex iron oxide dusts and fumes, as well as human clinical studies on aerosolized, micron-size iron oxide particles were discussed. They conclude that iron oxide particles have not been described to elicit acute inhalation response nor promote lung disease after chronic exposure. Further, the few human clinical studies comparing inhalation of fine and ultrafine metal oxide particles report no acute changes in the health parameters measured.

MCA Recommendation

Considering the above data, the MCA does not agree that further study involving a review of the available carcinogenicity data for iron oxides is required. Such review has already been undertaken and the determination is that iron oxides are not human carcinogens. The MCA thus believes that the proposed TWA-WES value of 5 mg/m^3 for the respirable fraction should be maintained.

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25. ISOCYANATES, (POLY-) (as NCO)

SWA recommends that the TWA-WES for isocyanates (including TDI, 2,6-TDI, HDI, IPDI, MDI & HMDI) be reduced from 0.02 mg/m^3 to 0.0001 mg/m^3 (0.1 µg/m^3), as an interim value, removing the STEL value of 0.07 mg/m^3. This revision aims to reduce the risk of occupational asthma and to protect for irritation of the eyes and mucous membranes in exposed workers. No reason is given for not recommending a STEL value.

The SWA evaluation used the term 'isocyanates' for those compounds that possess either 2 (diisocyanates) or 3 (triisocyanates) functional groups, sometimes called polyisocyanates. SWA recommends a priority in-depth assessment of the toxicological and epidemiological data for this group of chemicals.

The proposed interim TWA value is consistent with the HCOTN (2018) recommendation.

SWA notes that the recommended value is quantifiable through available sampling and analysis techniques, with which the MCA are uncertain.

As per the Gestis database for international limit values, there are only four countries with a limit value for isocyanates (all; as -NCO). The TWA value is 0.02 mg/m^3, while the STEL ranges from 0.02 to 0.07 mg/m^3. There are then limit values for the various types of isocyanates, as follows:

- Toluene diisocyanate (TDI) – 19 countries; TWA = 0.007 to 0.1 mg/m^3, with 67 percent at 0.034 to 0.035 mg/m^3 (0.005 ppm) and STEL = 0.003 to 0.2 mg/m^3, with 61 percent at 0.14 to 0.17 mg/m^3 (0.02 ppm)
- Hexamethylene diisocyanate (HDI) – 20 countries; TWA = 0.02 to 0.075 mg/m^3, with 67 percent at 0.035 to 0.037 mg/m^3 (0.005 ppm) and STEL = 0.03 to 0.15 mg/m^3, with 33 percent at 0.035 mg/m^3 (0.005 ppm)
- Methylene bisphenyl isocyanate (MDI) – 18 countries; TWA = 0.02 to 0.1 mg/m^3, with 83 percent at 0.05 to 0.052 mg/m^3 (0.005 ppm) and STEL = 0.05 to 0.2 mg/m^3, with 38 percent at 0.2 mg/m^3 (0.02 ppm).

Comment on toxicological information and data

SWA notes that the toxicology of polyisocyanates is very similar, with the critical effects being asthma due to sensitisation and irritation of the skin, mucous membranes, eyes and respiratory tract. There is also the potential for both irritant and allergic contact dermatitis. No difference in potency for the different polyisocyanates has been identified based on the available epidemiological data (ACGIH, 2018; HCOTN, 2018). In addition, while much is unclear about the mechanism(s) by which isocyanates cause allergic reactions, not only inhalation of isocyanates, but also skin contact can contribute to the development of allergic complaints. It is clear that the reactive NCO-groups, present in all isocyanates, play a role (HCOTN, 2018).

Based on current knowledge, Roberge et al (2017) notes that it is not possible to determine whether isocyanate sensitisation is caused solely by very high exposure or whether repeated low-dose exposures over a long time can also lead to asthmatic sensitisation. Continuous rather than intermittent exposure to isocyanates seems to increase the risk of developing occupational asthma. Once sensitised, the worker will react to very low concentrations. Roberge et al (2017) further notes that current literature suggests that an average exposure of less than 0.005 ppm (0.035 – 0.05 mg/m^3, depending on type of isocyanate) and peaks of less than 0.020 ppm (0.15 – 0.2 mg/m^3) in total isocyanate functional groups (NCO-groups) lead to an annual occupational asthma incidence of less than 1 percent in non-sensitised workers. This is consistent with the ACGIH (2018) finding that since the mid-1970s, annual occupational asthma incidence rates have been less than 1 percent against measured 8-hour workplace TDI concentrations of less than 0.005 ppm (0.035 mg/m^3). It is also reflected in the German limits reviewed by SWA.

A critical review of the ACGIH 2016 documentation for reduction of the TDI TLVs™ from a TWA value of 0.005 mg/m^3 to 0.001 mg/m^3, and from a STEL value of 0.02 mg/m^3 to 0.005 mg/m^3, concludes that they were 'unlikely to result in fewer cases of occupational asthma' and 'not adequately supported' (Lynch et al, 2018). Specifically, Lynch et al (2018) believe that the ACGIH 2016 documentation does not fully consider or integrate the results of all the available human and animal studies, and the results of the studies published between the 2004 and 2016 ACGIH reviews were similar to previous studies and thus did not indicate that the TDI TLVs should have been changed.

HCOTN (2018) established an exposure-response relationship using data from two studies in workers exposed to HDI and one study of workers exposed to TDI. This was used as the basis of deriving a concentration that corresponds with an extra risk of 1 percent for occurrence of adverse effects of the air ways characteristic of occupational asthma. They appear to have focussed on the adverse effects on the airways that can occur after sensitisation to isocyanates. HCOTN (2018) notes that the human studies that they used to derive their value had limitations.

HCOTN (2018) reviewed a large number of epidemiological studies, but only used the data from a select few (Collins et al, 2017; Pronk et al, 2007 & 2009) to derive their risk value. Overall, effect levels have been reported in a broad range from 100 (the upper cut-off level of the evaluation) down to less than 1 µg NCO/m^3. In fact, there were only three studies with an effect at less than 1 µg NCO/m^3. Most studies that detected an effect were above 1 µg NCO/m^3. In addition, dermal exposure and subsequent sensitisation via the skin could generally not be excluded as a contributing factor.

ECHA (2019) reviewed a large range of international evaluations of diisocyanates, including those by ACGIH, HCOTN, ATSDR, DFG, etc. They consider that it is appropriate to derive an exposure-response based on the concentration of the NCO-group and to apply that to all diisocyanates. ECHA however did not propose an exposure limit for diisocyanates, but recommended risk assessment to further develop the approach to derive an exposure response based on a weight of evidence assessment of three identified key documents presenting exposure responses for respiratory sensitisation. The three identified key documents describe the exposure-response by Daniels (2018) and Collins et al (2017) based on TDI exposure, which accounts for 60 percent of current diisocyanate use in Europe, and by Pronk et al (2007, 2009) predominantly based on HDI exposure, which accounts for 4 percent of current use in Europe.

Overall ECHA (2019) notes that none of the dose-responses addressed the effect of peak exposures or included dermal exposure. They consider that, when using the exposure-responses they described to establish an exposure limit (8-hour TWA), subsequently, a STEL of not more than 5 times higher than that TWA value should be established. They also conclude that no Biological Limit Value (BLV) or Biological Guidance Value (BGV) can be established.

Comment on measurement and analysis

The highly reactive nature of isocyanate compounds and their low occupational exposure limits put high demands on both sampling and analytical techniques for monitoring them in air. The most common devices for sampling isocyanates are impingers and impregnated filters. Impingers are the least desired for personal sampling due to the risk of exposure to solvent vapours during sampling and other issues (e.g. glass breakage & difficulty with shipping the needed reagents). Existing impregnated filter devices are safer for the worker to wear, but also have known issues (Streicher et al, 2002; Merck, 2018).

According to White (2006), Methods for the Determination of Hazardous Substances (MDHS) 25/3 (now MDHS 25/4) is the method probably most commonly used worldwide for the determination of organic NCO in air, but it is considered not particularly well suited to workplace conditions and the chemical analysis is complex. It is widely held that the collection and analysis of air samples requires considerable expertise (White, 2006), which tends to make the procedure relatively costly. The qualitative and quantitative limits of detection (LOD / LOQ) for isocyanate using MDHS 25/4, defined as three times and ten times the standard deviation of six blank determinations, have been found to

be typically around 0.001 and 0.004 µg NCO per sample respectively (EC detection). For a 15-litre air sample, these figures correspond to qualitative and quantitative detection limits of 0.07 µg/m^3 and 0.27 µg/m^3 respectively.

The estimated LOD of NIOSH Analytical Method number 5522 for the isocyanates 2,4-TDI, 2,6-TDI, MDI and HDI are 0.1, 0.2, 0.3 and 0.2 µg per sample, respectively. The level of quantitation (LOQ) will be higher. For OSHA Sampling and Analytical Method numbers 42 (diisocyantes - HDI, 2,4-TDI, 2,6-TDI) and 47 (MDI), the overall procedure LOD is: 2,6-TDI = 1.6 µg/m^3; HDI = 2.3 µg/m^3; 2,4-TDI = 1.3 µg/m^3; and MDI = 0.8 µg/m^3. The reliable LOQ is calculated at: 2,6-TDI = 2.3 µg/m^3; HDI = 2.9 µg/m^3; 2,4-TDI = 2.5 µg/m^3; and MDI = 2.6 µg/m^3. The LOQ for these methods is around an order of magnitude higher than that for MDHS 25/4.

Creely et al (2006), in a paper originating from a comprehensive study of isocyanate users in the UK covering the motor vehicle repair sector and other industries, determined personal exposure to isocyanates measuring airborne concentrations according to MDHS 25/3 and via biological monitoring. Creely et al (2006) and Jones (2019) note that biological monitoring by analysis of metabolites in urine can be a relatively simple and inexpensive way to assess exposure to isocyanates, as well as being a useful way to evaluate the effectiveness of control measures in place.

The ASSET™ EZ4-NCO dry sampler (Merck, 2018) is claimed to be the superior sampling device for measurement of isocyanates in air. It uses dibutyl amine (DBA) derivatisation of isocyanates according to ISO 17734-1 (DBA derivatives are very stable) and the special sampler design ensures that both the vapour phase and particulate isocyanates are captured and derivatised during sampling. The analytical method can successfully reach a LOQ of 5 ng/mL for most isocyanates in the final sample when using LC-MS-MS analysis and a LOQ of 10 ng/mL when LC-MS analysis is used. These numbers translate, respectively, to 0.21 µg/m³ of isocyanates and 0.42 µg/m³ in air if a 24-litre air sample was taken. Based on a 96-litre air sample, the lowest LOQ might get to 0.05 µg/m^3.

When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission (2017) state that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA.'

Airborne isocyanate concentrations have been found to be generally very low (range 0.0005 - 0.066 mg/m^3). Creely et al (2006) found a total of 50 of the 70 samples they collected were less than 0.001 mg/m^3, their LOQ for MDHS 25/3, hence assigned a value of half the LOQ (0.0005 mg/m^3). Of the 70 samples, 67 were below the UK workplace exposure limit of 0.02 mg/m^3. The highest inhalation exposures occurred during spray painting activities in a truck manufacturing company (0.066 mg/m^3) and also during spray application of polyurethane foam insulation (0.023 mg/m^3).

MCA Recommendation

Given the following guidance in the SWA (2019) publication:

> Exposure standards do not identify the dividing line between a healthy and unhealthy work environment. Natural biological variation and the range of individual susceptibilities mean a small number of people may experience adverse health effects below the exposure standard. Sections 17 and 19 of the WHS Act together require that exposure to substances in the workplace is kept as low as is reasonably practicable,

the MCA believes that the TWA-WES should be based on preventing the sensitisation of workers. If this is the case, then the current TWA-WES may be sufficiently protective, particularly where medical surveillance is also required to detect susceptible / sensitised individuals. The MCA however agrees that further in-depth assessment of this WES is required.

The MCA believes that medical surveillance is required to detect susceptible / sensitised individuals. Biological monitoring is also recommended to check on the efficacy of controls, primarily respiratory protection and for skin contamination.

In fact, given the complex aspects of isocyanates toxicity and exposure assessment, rather than depend on just an in-air regulatory exposure limit (WES), the MCA believes it would be best to have an industry-specific guidance / best practice approach. Such approaches already exist, including the program described by Gannon et al (2005), which has the goals of prevention, early detection and mitigation of effect of key endpoints, especially asthma and to a lesser degree dermatitis, in people who are occupationally exposed, or potentially exposed, to isocyanates and products containing isocyanates.

The issue of use of isocyanates from 2-pack paints and polyurethane resins in mining has been described in various government publications, such as the Safety Bulletin (74) published in November 2007 by the Queensland Mines Inspectorate. Other useful guidance material is as follows:

- The SWA Guide to Handling Isocyanates
- The UK HSE websites Controlling hazardous substances – Construction isocyanates: Spraying and Solutions from HSE - Isocyanates
- The IRSST Guide for Safe Use of Isocyanates – An Industrial Hygiene Approach.

SWA also needs to clarify quantification of the recommended value with currently available sampling and analysis techniques available in Australia.

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26. MANGANESE, FUME, DUST & COMPOUNDS (as Mn)

SWA recommends that the TWA-WES for manganese compounds (fume & dust) (as Mn) be reduced from 1 mg/m^3 to 0.02 mg/m^3 (respirable fraction) and 0.1 mg/m^3 (inhalable fraction), removing the STEL value of 3 mg/m^3. This revision aims to protect against adverse neuro-physiological and neuro-psychological effects in exposed workers. The STEL was not recommended as the TWAs were considered adequately protective for acute exposure to manganese fume. The proposed TWA values are consistent with the TLVs® recommended by the ACGIH (2018).

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.' Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Much of the Western world has set a TWA exposure limit for manganese compounds (as Mn) of between 0.02 and 5 mg/m^3, as per the Gestis database for international limit values, with most (38%) being set at 0.2 mg/m^3. In fact, the respirable fraction is often set at either 0.02 or 0.05 mg/m^3, while the inhalable fraction is often set at either 0.1 or 0.2 mg/m^3, reflecting the recommendations of the ACGIH (2018) or SCOEL (2011), respectively. STEL values are much fewer (only 9 countries), varying between 0.16 and 20 mg/m^3, with most (29%) being set at 3 mg/m^3.

Comment on toxicological information and data

SWA notes that manganese is an essential human trace element and important co-factor in many enzymes processes. Manganese exposure has been associated in some studies with adverse respiratory and cardiovascular effects; however, the neurological effects of manganese are considered to be the major concern for the establishment of occupational exposure limits (SCOEL, 2011).

High manganese exposures can result in severe neurotoxic signs and symptoms, some of which resemble those of idiopathic Parkinson's disease. This syndrome, which may also include psychiatric manifestations, is known as 'manganism'. The clinical symptoms associated with manganism, such as movement disorders and neurological dysfunction, have generally been reported at exposure levels above 5 mg/m^3 (SCOEL, 2011), although ATSDR (2012) notes that workplace inhalation exposure levels producing overt symptoms of manganism have been of the order of 2 to 22 mg/m^3. The critical effects in humans that are associated with exposure to manganese compounds and relevant to the currently recommended exposure limits, are non-clinical neurofunctional effects, such as extrapyramidal motor system effects (including fine tremors), which may lead to disorders clinically resembling Parkinson's disease.

O'Neal and Zheng (2015) note that individual factors such as age, gender, ethnicity, genetics and pre-existing medical conditions can influence an individual's susceptibility to manganese toxicity. They also note that emerging data suggest that, beyond traditionally recognised occupational manganism, manganese exposures and the ensuing toxicities occur in a variety of environmental settings, nutritional sources, contaminated foods, infant formulas, and water, soil and air with natural or man-made contaminations. In addition, once the signs and symptoms due to manganese neurotoxicity appear, they are usually irreversible and actually continue to progress, despite removal from the exposure scenario.

Harischandra et al (2019) note that while the body can efficiently remove excess manganese, primarily through the gut and liver, the brain cannot. Manganese toxicity is seen in the central nervous system mainly affecting nigrostriatal neuronal circuitry and subsequent behavioural and motor impairments. Harischandra et al (2019) note that recent reports suggest the involvement of

manganese in the misfolding of proteins such as α-synuclein and amyloid, thus providing credence to the theory that environmental exposure to toxicants can either initiate or propagate neurodegenerative processes by interfering with disease-specific proteins. Based on the current evidence, they propose a 'Manganese Mechanistic Neurotoxic Triad' comprising (1) mitochondrial dysfunction and oxidative stress, (2) protein trafficking and misfolding, and (3) neuroinflammation.

In arriving at their TLVs® for manganese, ACGIH (2018) gave consideration to the LOAELs derived from the studies of Bast-Pettersen (2004), Lucchini et al (1999), Mergler et al (1994) and Roels et al (1992), which are in the range of 0.03 to 0.04 mg/m^3 (respirable fraction). The respirable fraction is considered to be the best indicator of systemic availability (SCOEL, 2011; ACGIH, 2018).

SCOEL (2011) recommends exposure limits of 0.05 mg/m^3 (respirable fraction) and 0.2 mg/m^3 (inhalable fraction). They note that, because of the heterogeneity of the data (different types of industry, different manganese compounds and particle sizes, different study designs and different neurofunctional measurements), and the inherent limitations of every individual study, it is not possible to identify one single critical study that would be the best basis for setting an exposure limit. Some studies identified a LOAEL, others a NOAEL. Some studies relied on the respirable fraction; others on the inhalable or 'total' (thoracic) fraction. A global approach using the most methodologically-sound studies was therefore considered by SCOEL (2011) to be the most robust and reliable approach to setting a manganese exposure limit.

SCOEL (2011) used many of the same studies used by ACGIH, such as Roels et al (1992), Gibbs et al (1999), Myers et al (2003), Young et al (2005), Bast-Pettersen et al (2004), Ellingsen et al (2008) and Lucchini et al (1999), which showed adverse neurological effects and identified a point-of-departure in the dose-effect/response relationship relevant to an exposure limit. They further note that the reported changes in these studies are subtle early neurofunctional effects which are non-clinical in nature and are only detected at a statistical level between groups of workers. In addition, they note that their recommended exposure limits are conservative due to a number of factors.

ATSDR (2012) note that manganese airborne concentrations producing subclinical neurological effects in chronically exposed workers range from about 0.07 to 0.97 mg/m^3. Based on a neurological effect study of battery facility workers occupationally exposed to manganese (Roels et al, 1992), ATSDR (2012) derived a respirable manganese concentration of 0.142 mg/m^3 as the point of departure (considered approximately equivalent to a NOAEL) in deriving its Minimal Risk Level (MRL) for manganese for general population risk assessment.

Santamaria et al (2007) conclude that available data did not support an association between welding and clinical neurotoxicity, although manganism was observed in highly exposed workers. Bailey et al (2017) set out to derive a manganese exposure limit value for welders based on a review of studies that evaluated manganese exposure concentrations from welding fumes and:

- Neurological effects in welders
- Levels of manganese in the brains of welders (via pallidal index [PI] estimated from magnetic resonance imaging [MRI])
- Other biomarkers of manganese exposure in welders (i.e. blood & urine)
- Manganese brain concentrations, PI and corresponding neurological effects in non-human primates.

Their analysis suggests uncertainty in quantifying dose-response associations for manganese from many of the occupational welding studies. The few welding studies that adequately estimate exposure suggest a possible exposure limit of 0.10 to 0.14 mg/m^3 for respirable manganese. They note that this range is consistent with other epidemiology studies, studies of biomarkers of manganese exposure in welders, and with studies in non-human primates.

In a later review of scientific evidence related to potential toxicity of occupational exposure to airborne manganese, Bailey (2018) notes that, had ACGIH applied the most current scientific methodology (benchmark dose (BMD) modelling) to derive a no effect level from the Roels et al (1992) data, it would have derived a respirable manganese TLV® closer to 0.142 mg/m^3. Bailey (2018) concludes that overall, the best and most current available scientific evidence suggests that airborne occupational exposure to manganese as an 8-hour TWA of 0.14 mg/m^3 (and likely as high as 0.2 mg/m^3) for manganese in welding fumes would not produce adverse neurological effects in welders.

MCA Recommendation

Considering the above data, the MCA suggests that the SCOEL (2011) recommended exposure limits of 0.05 mg/m^3 (respirable fraction) and 0.2 mg/m^3 (inhalable fraction) would be more appropriate TWA-WESs for manganese and its compounds.

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27. NICKEL, METAL AND INSOLUBLE COMPOUNDS (as Ni)

SWA recommends that the TWA-WES for nickel compounds (metal & insolubles) (as Ni) be reduced from 1 mg/m^3 to 0.1 mg/m^3 (inhalable fraction), to protect against inflammation of the airways and to minimise the potential for lung and nasal cancer in exposed workers. This makes it the same as the value proposed (retained) for soluble nickel compounds, which is set to protect against pulmonary damage and possible carcinogenic effects in the respiratory system of exposed workers. The proposed TWA value is consistent with the limit value recommended by the AIOH (2016) for both soluble and insoluble compounds. The limit for the soluble compounds is also consistent with the TLV® recommended by the ACGIH (2018).

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA agrees.

Much of the Western world has set a TWA exposure limit for nickel compounds (as Ni) of between 0.005 and 1 mg/m^3 (most inhalable, but some respirable), as per the Gestis database for international limit values, with most (29%) being set at 0.1 mg/m^3. Often the limit varies depending on whether the Ni compound is soluble or insoluble, but not always. STEL values are much fewer (only 4 countries), varying between 0.02 and 2 mg/m^3.

Comment on toxicological information and data

SWA notes that the critical effect of nickel exposure is respiratory cancer for both soluble and insoluble compounds, plus inflammatory responses in the lung for the insoluble compounds. Nickel compounds have long been recognised as causing cancers of the lung, nasal cavity and paranasal sinuses, and of being a sensitiser. The compounds principally implicated in causing respiratory cancer are sulfidic nickel, particularly nickel sub-sulfide (Ni_3S_2) and oxidic nickel, which includes a range of insoluble nickel compounds. There is debate about whether soluble nickel compounds are carcinogenic (AIOH, 2016).

One of the most extensive studies on nickel exposures was carried out at Clydach Refinery in South Wales. This study followed 2521 men who had worked at the refinery for more than 5 years between 1902 and 1969. It showed clear evidence of nasal and lung cancer. These workers had been exposed to 'relatively high' concentrations of airborne nickel. As the workers were tracked over time and exposures were greatly reduced, follow-up studies demonstrated negligible risks from 'total nickel' at concentrations < 0.2 mg/m^3. It was also found from this study that it was difficult to assign a risk to individual forms of nickel. It is now known that the risk is greater when there is exposure to mixed species of nickel. Recent information has also indicated that exposure to relatively low concentrations of nickel via the oral route (ingestion) can exacerbate adverse health effects in nickel-sensitised individuals (AIOH, 2016). The occurrence of multiple Ni species in most work environments and the difficulty in speciation for analysis suggest a common limit for all species.

A precautionary guideline value of 10 µg/L nickel in urine is recommended as being more or less equivalent to sparingly soluble airborne nickel (Tomassen et al, 1999); above this may indicate work practices that are not best practice. Establishing a baseline using urinary nickel level can be used as a measure of control effectiveness for workplaces where inhalation, or skin contamination, hence inadvertent hand mouth contact and ingestion, may be an issue (i.e. electroplating) and drive continuous improvement.

MCA Recommendation

Considering the above data, the MCA agrees with the AIOH (2016) recommended exposure limit of 0.1 mg/m^3 for nickel (both soluble & insoluble). However, considering the carcinogenic effect, exposures should be controlled to as low as reasonably practicable (ALARP). In addition, biological monitoring (in urine) is also recommended to check on the efficacy of controls, primarily respiratory protection and for hand-to-mouth contamination.

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28. NITROGEN DIOXIDE (NO_2)

SWA recommends that the TWA-WES for nitrogen dioxide (NO_2) be reduced from 3 ppm to 0.2 ppm, removing the STEL value of 5 ppm, to protect against adverse effects in the lower respiratory tract in exposed workers. The STEL was not recommended as the TWA was considered adequately protective for acute exposure to NO_2. The proposed TWA value is consistent with the TLV® recommended by the ACGIH (2018) in 2012.

However, the ACGIH TLV's® are 'based solely on health factors' with 'no consideration of economic or technical feasibility.' Subsequently, the ACGIH® caution regulatory agencies against the application of TLV's® in regulations as they 'are not designed to be used as standards' (ACGIH, 2018), particularly in circumstances where reliable test methods have not been validated to measure workplace exposures at the TLV®.

SWA notes that the recommended value is readily quantifiable through currently available sampling and analysis techniques, with which the MCA are uncertain.

Much of the Western world has set a TWA exposure limit for NO_2 of between 0.5 and 3 ppm, as per the Gestis database for international limit values, with most (53%) being set at 3 ppm, although 42 percent are set at 0.5 ppm. The 0.5 ppm TWA value reflects the recommendation of SCOEL (2014). STEL values are common (19 countries), varying between 0.5 and 5 ppm, with most (43%, respectively) being set at either 5 or 1 ppm.

Comment on toxicological information and data

SWA notes that NO_2 is found in ambient air due to various processes and critical effects in humans that are associated with exposure to it include lower respiratory tract irritation and tissue damage. NO_2 is an important atmospheric trace gas and occupational exposures to it are relatively rare compared to outdoor and domestic exposures (WHO, 2000).

NO_2 is said to be detectable by humans as a pungent, acrid odour between 0.2 and 1 ppm. With slowly increasing concentrations the odour is not perceived until much higher concentrations have been reached, so the warning effect of the gas is poor under this condition. Irritation to the nose and throat occur between 20 and 30 ppm (SCOEL, 2014).

Although there are exceptions, the vast majority of lung biochemical studies in animals show effects only after acute or sub-chronic exposure to levels of NO_2 exceeding 2 ppm. Several types of animal study have indicated that NO_2 increases susceptibility to bacterial lung infections and perhaps viral infections. Studies with animals have also clearly shown that several weeks to months of exposure to NO_2 concentrations of less than 1 ppm cause a plethora of effects, primarily in the lung but also in other organs such as the spleen, liver and blood. Both reversible and irreversible lung effects have been observed (WHO, 2000).

Generally, NO_2 concentrations in excess of 1 ppm are necessary during acute controlled exposures to induce changes in pulmonary function in healthy adult humans. Because these concentrations almost never occur in ambient air, concern about the effects of NO_2 has been focused on people with pre-existing lung disease, with asthmatics likely being the most sensitive. There have been numerous studies of people with asthma, chronic obstructive pulmonary disease (COPD), or chronic bronchitis showing that exposure to low levels of NO_2 can cause small decrements in forced vital capacity and forced expiratory volume in 1 second (FEV_1) or increases in airway resistance. Pulmonary function responses have been shown in three studies of asthmatics exposed to 0.3 ppm while performing mild to moderate exercise. However, these results are not always consistent with other studies of asthmatics exposed to the same or higher NO_2 concentrations (WHO, 2000).

WHO (2000) concludes that, despite the large number of acute controlled exposure studies on humans, several of which used multiple concentrations, there is no evidence for a clearly defined concentration-response relationship for NO_2 exposure. However, given the small changes in lung

function (< 5% drop in FEV_1 between air and NO_2 exposure) and changes in airway responsiveness reported in several studies, 0.2 to 0.3 ppm is a clear lowest-observed-effect level.

The SCOEL (2014) documentation was based on compilations by WHO (1997), DECOS (2004), US EPA (2008), DFG (2005 and 2010), ACGIH (2012) and National Research Council of the National Academies (2012), with additional literature search performed in December 2013. SCOEL (2014) recommends a NO_2 TWA limit of 0.5 ppm based on lung function effects under chronic occupational exposures from an epidemiological study in hard coal miners, supported by animal study results. A STEL of 1 ppm is also recommended based on observed changes in the bronchoalveolar lavage fluid (initial signs of inflammatory reactions) in volunteers after a 3-hour exposure to NO_2 at 1.5 ppm and above. NIOSH and OSHA also recommend a STEL of 1 ppm.

Comment on measurement and analysis

The LOD for NO_2 as stated in OSHA Sampling and Analytical Method number 182 is calculated as being 0.07 ppm for a 3 L air sample, and a quantitative detection limit of 0.19 ppm for a 3 L air sample. For NIOSH Analytical Method number 6700, the LOD is said to be around 0.5 ppm for a TWA sample collected over 15 minutes. According to SCOEL (2014), chemoluminescence measurements are considered to represent the 'gold standard' of NO/NO_2 analysis, with a lowest detection limit of 0.002 ppm.

Current hand-held detection equipment for NO_2, the most common measurement method, say that they measure from 0 ppm with 0.1 ppm resolution (smallest detectable change). According to SCOEL (2014), there are new technology electrochemical sensors with a lower detection limit of 0.04 ppm. Gas detector tubes are said to read down to 0.1 ppm.

When assessing whether or not accurate sampling and analytical methods are available to measure exposure to compare with or assess compliance against a recommended exposure standard, the European Commission (2017) state that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA.'

Gamble et al (1987) collected samples of NO_2 and respirable particulate matter using personal samplers on 232 workers in four garages. They found a mean TWA of 0.23 ppm of NO_2 (with standard deviation of 0.24, range of 0.13 to 0.56). Ulfvarson et al (1987) used personal sampling and area sampling to measure NO_2 exposures to 17 bus garage workers. They found TWA exposures of 0.1 to 0.59 ppm.

MCA Recommendation

Considering the above data, the MCA suggests that the SCOEL (2014) recommended exposure limits of a TWA of 0.5 ppm and a STEL of 1 ppm would be more appropriate WESs for NO_2. In addition, medical surveillance is required in the event of susceptible individuals.

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