Workplace Exposure Standard (WES) review

FORMALDEHYDE
(CAS NO: 50-00-0)

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New Zealand Government

WORKSAFE
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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for formaldehyde should be changed.

It considers the potential for exposures to formaldehyde in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for formaldehyde, which is currently set at a **WES-TWA** of 0.5**ppm** [8-hour shift], 0.33ppm [12-hour shift] with a **WES-Ceiling** value of 1ppm, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: methanal; formic aldehyde; methaldehyde; oxymethylene; methylene oxide; formalin [aqueous solutions]; FA.

2.0 Chemical and physical properties

Formaldehyde is a colourless gas with a strong, pungent, irritating odour (**ACGIH**®, 2017).

Formaldehyde has an odour threshold reported at less than 0.5ppm (ACGIH®, 2017).

Chemical and physical properties of formaldehyde include:

Molecular weight	30.03g/mol
Formula	CH_2O
Specific gravity	0.815 at 20°C
Melting point	-92°C
Boiling point	-19.5°C at 760 torr
Vapour pressure	10 torr at -88°C
Saturated vapour pressure	13,000ppm at -88°C
Relative vapour density [air = 1]	1.08
Flash point	Closed cup: 83°C [37% aqueous solution – methanol free]; 50°C [aqueous solution with 15% methanol]
Explosive limits	Lower: 7%; Upper: 73% by volume in air.
Autoignition temperature	430°C
Solubility	Very soluble in water [55g/100mL]; soluble in alcohols and ether
Reactivity	Reactive and readily polymerises at room temperature; decomposition products include carbon monoxide and carbon dioxide
Conversion factors	1mg/m³ = 0.81ppm 1ppm = 1.23mg/m³ [25°C; 760 torr]

ACGIH®, 2017; **SCOEL**, 2017; **DECOS**, 2003

TABLE 1: Physicochemical properties of formaldehyde

Health-related hazard classifications for formaldehyde:

	HSNO CLASSIFICATION
Substance	Formaldehyde [>25% aqueous solution, with ≤10% methanol]
Classification	6.1B (All); 6.1C (O); 6.1C (D); 6.1B (I); 6.5B; 6.6B; 6.7A; 6.9B (All); 6.9B (O); 6.9B (1) 8.2C; 8.3A

TABLE 2: **HSNO** health-related hazard classifications of formaldehyde (**EPA**, 2019)

For a full listing of all **HSNO** health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Derman exposure route.

[I] Inhalation exposure route.

3.0
Uses

Formaldehyde is predominantly used as a chemical intermediate.

Particularly in the production of phenolic, urea and melamine resins that have wide uses as adhesives and binders in wood production; pulp and paper; and the synthetic vitreous fibre industry; in the production of plastics and coatings; and, in textile finishing. Formaldehyde is also used in the manufacture of industrial chemicals. As formalin, aqueous solutions of formaldehyde are used as disinfectants and preservatives with many applications (SCOEL, 2017; ACGIH®, 2017).

Formaldehyde is an endogenous substance formed naturally in humans and other lifeforms through amino acid catabolism (**ANSES**, 2018). Formaldehyde is ubiquitous in the environment due to this endogenous production; formation during the combustion of organic material; formation from the breakdown of hydrocarbons in the air; and, releases into the environment (SCOEL, 2017).

Occupational exposure to formaldehyde can occur during production, storage, transportation and end-use.

Workers can be exposed to formaldehyde gas, vapour or liquid [when in solution] via inhalation and eye or dermal contact.

The number of workers exposed or potentially exposed to formaldehyde in New Zealand workplaces is unknown.

Statistics New Zealand 2018 data indicate that 23,650 New Zealand workers were working in the areas of:

- veneer and plywood manufacture
- reconstituted wood product manufacturing
- pulp, paper and converted paper product manufacturing
- chemical manufacturing
- basic polymer manufacturing
- cleaning compound and toiletry preparation manufacturing
- polymer product manufacturing
- funeral, crematorium and cemetery services (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The ANSES review of formaldehyde noted that while serious acute effects, such as respiratory difficulties, oedema and lung congestion, could be observed above 12,000**µg/m³** [9.72ppm], the most sensitive endpoints at lower concentrations were irritant effects (ANSES, 2018).

The ACGIH® review of formaldehyde noted that:

> "Severe tracheobronchitis had occurred after inhalation of high concentrations, and contact with the vapor or liquid could cause superficial coagulative necrosis. Allergic reactions and the induction of asthma-like conditions have been reported after occupational exposures. Exposure to high concentrations in air could produce spasms and edema of the larynx. Individual susceptibility to the irritating effects of airborne formaldehyde could decrease with repeated exposures."
>
> "Free formaldehyde (0.5%) as part of phenol-formaldehyde resins has been associated with severe skin necrosis, respiratory distress, and cardiovascular and kidney toxicities after a large, acute dermal exposure (Cohen *et al*., 1989). Lightheadedness, dizziness, disturbed equilibrium, and diminished dexterity (as measured by performance on pegboard tests) have been associated with occupational formaldehyde exposures among histology laboratory technicians (Kilburn *et al*., 1987)." (References cited in ACGIH®, 2017).

The New Zealand EPA classifies formaldehyde as a 6.1B, 6.1C and 6.9B substance – a substance that is acutely toxic and harmful to human target organs or systems, respectively (EPA, 2019).

The ANSES [2018], SCOEL [2017] and ACGIH® [2017] reviews all cited the volunteer exposure study by Lang *et al*. (2008 cited in ANSES, 2018; SCOEL, 2017; ACGIH®, 2017) as key to the establishment of the **NOAEC** from which **OELs** were derived. A similar volunteer exposure study by Mueller *et al*. (2013 cited in ANSES, 2018; SCOEL, 2017; ACGIH®, 2017) was considered key by SCOEL [2017] and supportive by ANSES [2018] and ACGIH® [2017]. The ANSES review of formaldehyde summarised the two studies:

> "The study by Lang *et al*. (2008) was conducted with 21 volunteers (11 male and 10 female). Measurements consisted in conjunctival redness, blinking frequency, nasal resistance and flow, and pulmonary function. Ten different exposure conditions, described below, were put in place, corresponding to different concentrations of formaldehyde in air. Exposure lasted four hours and included or excluded peaks over a 15 minutes period:
>
> – 0**µg.m^{-3}**; 185µg.m^{-3}; 369µg.m^{-3}; 615µg.m^{-3}
> – 369µg.m^{-3} + four 738µg.m^{-3} peaks; 615µg.m^{-3} + four 1230µg.m^{-3} peaks
> – with masking agent (ethyl acetate): 0µg.m^{-3}; 369µg.m^{-3}; 615µg.m^{-3}; 615µg.m^{-3} + four 1230µg.m^{-3} peaks.
>
> "All the subjects were exposed to each of the exposure conditions. No significant changes were reported following exposure to formaldehyde for nasal resistance and flow, pulmonary function, or reaction time. Regarding conjunctival redness, the only statistically significant observation was found at the highest exposure level of 615µg.m^{-3} + four 1230µg.m^{-3} peaks. The increase in blinking frequency became significant with the same exposure condition, also with the masking agent. Subjective effects (ocular, nasal, respiratory irritation, olfactory symptoms, discomfort) occurred from 369µg.m^{-3} but were not always significant with the masking agent.

"The study by Mueller *et al*. (2013) was conducted with 41 male volunteers. The measured effects were conjunctival redness, eye blinking frequency, tear film breakup time (reflecting ocular dryness) and nasal flow. ANOVA was used for the statistical analysis with a repeated-measures cross-over design. Five different exposure conditions, described below, were put in place. Exposure lasted four hours and included or excluded peaks over a 15 minutes period:

- 0μg.m^{-3}; 615μg.m^{-3}; 861μg.m^{-3}
- 369μg.m^{-3} + four 615μg.m^{-3} peaks; 492μg.m^{-3} + four 984μg.m^{-3} peaks.

"All the subjects were exposed to each of the five exposure conditions for five consecutive days. It should be noted that this study divided the volunteers into "hypersensitive" and "hyposensitive" groups, using a test of sensitivity to CO_2.

"No significant changes were observed regarding conjunctival redness or eye blinking frequency compared to the controls. Tear film breakup time was reduced in the "hyposensitive" subjects exposed to 369μg.m^{-3} + four 615μg.m^{-3} peaks and 861μg.m^{-3} compared to the controls. However, no dose-response relationship was seen and the same observations were not found with the "hypersensitive" subjects. Similarly, nasal flow increased only at 369μg.m^{-3} + four 615μg.m^{-3} peaks for "hyposensitive" subjects. Regarding subjective effects, no statistically significant difference was reported for the nasal and ocular irritation tests. For olfactory symptoms and the perception of "impure air", an increase in effects, primarily in "hypersensitive" subjects, was observed." (References cited in ANSES, 2018).

The New Zealand EPA classifies formaldehyde as an 8.2C and 8.3A substance – a substance that is corrosive to dermal tissue and ocular tissue, respectively (EPA, 2019).

The **NIOSH** Skin Notation Profile for formaldehyde/formalin summarised potential skin effects:

"No *in vivo* human studies were identified that estimated the percent absorption of formaldehyde following dermal exposure. However, data on *in vivo* toxicokinetics in animals suggest that formaldehyde has limited potential to be absorbed through the skin (that is, percent absorption of less than 10%). Although a nonstandard chronic study and a nonstandard developmental dermal toxicity study suggest that the substance is not likely to be a systemic or developmental toxicant at the doses tested, formaldehyde exposure to a large area of the skin has resulted in severe skin lesions with multisystem effects, including renal, cardiovascular, and lung impairments [Cohen *et al*. 1989]. The lack of toxicokinetic data needed to determine the extent of absorption and lack of standard animal studies of toxicity after dermal administration preclude evaluation of the systemic toxicity potential of formaldehyde by the dermal route. A case report provides some evidence of the potential of formaldehyde to be corrosive to the skin. However, data from several skin irritation studies in animals [Celanese Chemical Company Inc. 1972; Wahlberg 1993; Sekizawa *et al*. 1994; Fischer *et al*. 1995; Trattner *et al*. 1998] indicate that solutions of formaldehyde at concentrations up to 37% are likely to cause mild to moderate skin irritation. Concentrations above 37% may cause severe irritation or corrosion. Numerous reports of cases of occupational exposure [Cronin 1991; Bell and King 2002; Skotnicki-Grant 2006], historical patch-testing in humans [Meding and Swanbeck 1990; Fischer *et al*. 1995; Kiec-Swierczynska 1996; Marks *et al*. 1998; Beliauskiene *et al*. 2010], repeated-

> application testing in humans [Jordan *et al*. 1979; Flyvhom *et al*. 1997; Scheman *et al*. 1998], and positive responses in predictive tests in animals (including **GPMT**s, Buehler tests, and **LLNA**s) [Buehler 1965; Magnusson *et al*. 1969; Goodwin *et al*. 1981; Guillot *et al*. 1983; Andersen *et al*. 1985; Hilton *et al*. 1996] provide sufficient information on the potential of formaldehyde or formaldehyde-releasing chemicals in resins, fabrics, facial tissues, cosmetics, and cleaning agents to cause skin sensitization. Therefore, on the basis of the data for this assessment, formaldehyde is assigned the notation **SK: DIR (IRR)-SEN**." (References cited in NIOSH, 2011).

The New Zealand EPA classifies formaldehyde as a 6.5B substance – a substance that is a contact sensitizer (EPA, 2019).

The ANSES review of formaldehyde summarised the potential for respiratory sensitisation:

> "Regarding respiratory sensitisation, the study results are inconsistent.
>
> "Some studies showed a potentiating effect of formaldehyde on immediate and delayed bronchial response during exposure to allergens (Casset *et al*., 2006). Moreover, delayed response and asthma were found to be significantly more severe after inhalation of formaldehyde (Casset *et al*., 2006; Marchand, 2005).
>
> "However, several recent reviews of the literature relating specifically to the indoor air of homes or occupational environments led to the conclusion that respiratory sensitisation caused by formaldehyde was highly unlikely, in particular at low concentrations (**MAK**, 2014; Golden, 2011; Schram-Bijkerk *et al*., 2013). In fact, the associations between formaldehyde and respiratory symptoms may have been due to the influence of co-exposure or confounding factors such as psychosocial factors." (References cited in ANSES, 2018).

Repeated exposures to formaldehyde result in similar irritant effects reported during acute exposures: eye; throat and respiratory tract irritation; fatigue; and, headaches with symptoms occurring from 120µg/m^3 (**IPCS**, 2002; Ritchie *et al*., 1987 cited in ANSES, 2018).

The ANSES review of formaldehyde summarised the potential for reproductive toxicity:

> "Duong *et al*. (2011) conducted a systematic review of the data on the reproductive and developmental effects of formaldehyde as well as a meta-analysis. The results of this meta-analysis (which were consistent with those of the meta-analysis by Collins *et al*., 2001) showed that maternal exposure to formaldehyde was associated with a risk of spontaneous abortion. The authors themselves specify that confounding factors (co-exposure with other compounds that can induce effects on reproduction in the studies, and non-adjusted relative risks – **RR**s) and recall biases may have caused these RRs to be overestimated, but they did not consider they were able to assess them (Duong *et al*., 2011)." (References cited in ANSES, 2018).

The New Zealand EPA classifies formaldehyde as a 6.6B substance – a substance that is a suspected human mutagen (EPA, 2019).

Animals

The SCOEL review of formaldehyde summarised the potential for irritation after acute exposures:

> "Studies of the sensory irritation caused by formaldehyde in mice and rats showed the mouse to be markedly more sensitive (Barrow *et al*., 1983, 1986, Chang *et al*., 1981; Chang and Barrow, 1984). The concentration, which after short-term exposure leads to a reduction in the respiration rate to 50 % (**RD50**) in mice, was found to be between 3 and 5ppm (Chang *et al*. 1981, Schaper 1993). A clear no-effect level for nasal irritation in mice was found to be at 0.3ppm (Nielsen *et al*., 1999). In rats, RD50 values between 10 and 30ppm have been reported (Cassee, 1995; Cassee *et al*, 1996; Chang *et al*, 1981; Chang and Barrow, 1984; Schaper, 1993)." (References cited in SCOEL, 2017).

The SCOEL review of formaldehyde summarised the potential for sensitisation:

> "Results of studies in laboratory animals have indicated that formaldehyde may enhance their sensitization to inhaled allergens. In female BALB/c mice sensitized to ovalbumin, the serum titre of **IgE** anti-ovalbumin antibodies was increased approximately 3-fold in animals pre-exposed to 2.0**mg FA**/m^3 for 6h/day on 10 consecutive days. Similarly, exposure of female Dunkin-Hartley Guinea pigs, sensitized to airborne ovalbumin, to 0.3mg FA/m^3 produced a significant 3-fold increase in bronchial sensitization, as well as a significant 1.3-fold increase in serum anti-ovalbumin antibodies (IPCS 2002)." (Reference cited in SCOEL, 2017).

The SCOEL review of formaldehyde summarised the potential for specific organ toxicity after repeated exposure:

> "In rats exposed to FA concentrations of 10ppm, daily for 6 hours on 5 days a week, rhinitis, hyperplasia and squamous metaplasia of the respiratory epithelium of the nasal mucosa were described in all studies. In rats exposed to 1.0ppm for 2 years no histopathological changes were observed (no observed adverse effect concentration, NOAEC; Woutersen *et al*., 1989). From concentrations of 2ppm, rhinitis, epithelial dysplasia and even papillomatous adenomas and squamous metaplasia of the respiratory epithelium of the nose were found, from 6ppm squamous cell carcinomas (Kerns *et al*, 1983; Swenberg *et al*, 1980). At this concentration also the cell proliferation rate in the nasal mucosa was increased transiently, and from 10ppm increased permanently (Monticello *et al*, 1996).
>
> "Uninterrupted exposure of rats for 8 hours/day ("continuous") was compared with 8 exposures for 30 minutes followed by a 30-minute phase without exposure ("intermittent") in two 13-week studies with the same total dose. Effects were seen only after intermittent exposure to FA concentrations of 4ppm, but not after continuous exposure to 2ppm. The authors concluded that the toxicity in the nose depends on the concentration and not on the total dose (Wilmer *et al*, 1989). In mice exposed to FA concentrations of 2.0, 5.6 or 14.3ppm for 2 years (6 hours/day, 5 days/week), rhinitis and epithelial hyperplasia was observed, from 5.6ppm dysplasia, metaplasia and atrophy. Squamous cell carcinomas were observed only after concentrations of 14.3ppm (Kerns *et al*, 1983).

> "In hamsters exposed to FA concentrations of 10ppm (5 hours/day, 5 days per week) for life, survival was reduced and the incidence of hyperplasia and metaplasia (4/88, 5%) was slightly increased, but not that of tumours (Dalbey, 1982).
>
> "In Cynomolgus monkeys exposed almost continuously to FA concentrations of 0.2, 1 or 3ppm for 26 weeks, metaplasia and hyperplasia were observed in 1/6 and 6/6 animals of the 1 and 2ppm groups, respectively. In the animals exposed to concentrations of 0.2ppm, no histopathological changes were found (Rusch *et al*, 1983a, 1983b).
>
> "Reduced body weight gains were reported in rats exposed to FA concentrations from 10ppm for 6 hours a day in a 13-week inhalation study (Woutersen *et al*, 1987) and in those exposed to concentrations from 5.6ppm in a 2-year inhalation study (Kerns *et al*, 1983; Swenberg *et al*., 1980). In mice, reduced body weight gains were found in a 13-week inhalation study only at concentrations from 20ppm. Other systemic effects were not observed in these studies. Only in a 26-week inhalation study with continuous exposure (22 hours a day, 7 days a week) were reduced absolute and relative liver weights observed from concentrations as low as 3ppm (in addition to reduced body weight gain and lesions in the nasal region) (Rusch *et al*., 1983a, 1983b).
>
> "The findings in rats were reconfirmed after exposure of male F344 rats to concentrations of 0, 0.5, 1, 2, 6, 10 and 15ppm (6h/d, 5 d/week over 4 weeks). At 10 or 15ppm clear site-specific pathological changes (focal epithelial degeneration, inflammation and squamous metaplasia) were observed in a decreasing gradient (anterior to posterior) (Speit *et al*, 2011a).
>
> "A study related to the possible induction of lympho-haematopoetic neoplasms has been carried out in Fischer-344 rats and B6C3F1 mice at exposure concentrations between 0.5 and 15ppm over 4 weeks (Kuper *et al*., 2009). Nasopharynx-associated lymphoid tissues (NALT) and upper-respiratory tract-draining lymph nodes were studied by standard histopathology and immunohistochemistry for cell proliferation. The only effect noted was simple hyperplasia and increased proliferation rate of the lympho-epithelium of rats at 15ppm. Therefore the study did not support the hypothesis that FA may induce such systemic neoplasms by reaction with local lymphoid cells." (References cited in SCOEL, 2017).

The SCOEL review of formaldehyde summarised the potential for reproductive toxicity:

> "As FA has been shown not to reach tissues far of the site of first contact, that is, the upper respiratory tract after inhalation, data concerning these endpoints will not be reviewed here in detail. For a documentation of available studies reference can be made to a recent review of Nielsen *et al*. (2013).
>
> "The lack of the effects was supported by a review and meta-analysis (Collins *et al*. 2001). This review concluded that there was no convincing evidence of reproductive or developmental toxicity in animal studies at FA exposures by routes, which were relevant for risk assessment of workplace exposure levels." (References cited in SCOEL, 2017).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] evaluation of formaldehyde concluded that:

> There is *sufficient evidence* in humans for the carcinogenicity of formaldehyde. Formaldehyde causes cancer of the nasopharynx and leukaemia. Also, a positive association has been observed between exposure to formaldehyde and sinonasal cancer.
>
> There is *sufficient evidence* in experimental animals for the carcinogenicity of formaldehyde.

The Working Group was not in full agreement on the evaluation of formaldehyde causing leukaemias in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited. Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukaemia and myelodysplastic syndrome, with supporting information suggesting a decrease in the major circulating blood-cell types and in circulating haematological precursor cells. The authors and Working Group felt that this study needed to be replicated.

With an overall evaluation that:

> Formaldehyde is carcinogenic to humans (Group 1) (IARC, 2012).

The New Zealand EPA classifies formaldehyde as a 6.7A substance – a substance that is a known or presumed human carcinogen (EPA, 2019).

The US National Toxicology Program [**NTP**] Report on Carcinogens [**RoC**], Fourteenth Edition concluded that:

> "Formaldehyde is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans and supporting data on mechanisms of carcinogenesis. Formaldehyde was first listed in the Second Annual Report on Carcinogens in 1981 as reasonably anticipated to be a human carcinogen based on sufficient evidence from studies in experimental animals. Since that time, additional cancer studies in humans have been published, and the listing status was changed to known to be a human carcinogen in the Twelfth Report on Carcinogens (2011)." (NTP RoC, 2016).

Humans

The US NTP RoC Profile on formaldehyde summarised the rationale for listing formaldehyde in the RoC as "known to be a human carcinogen":

> "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia."

Nasopharyngeal cancer

"Evidence that formaldehyde causes nasopharyngeal cancer comes from (1) consistent findings of increased risk among individuals with the highest formaldehyde exposure in numerous case-control studies (Vaughan *et al*. 1986, 2000, Roush *et al*. 1987, West *et al*. 1993, Hildesheim *et al*. 2001), (2) excess cancer mortality associated with formaldehyde exposure in the **NCI** cohort of industrial workers (Hauptmann *et al*. 2004), and (3) findings of positive exposure-response relationships in a large multi-center case-control study (Vaughan *et al*. 2000) and in the NCI cohort (Hauptmann *et al*. 2004).

"The multi-center case-control study by Vaughan *et al*. (2000) is especially informative, because it had the largest number of cancer cases in formaldehyde-exposed individuals, and the analysis was stratified by histological subtype and used several different measures of exposure to evaluate risk. In this study, formaldehyde exposure was associated with differentiated squamous-cell carcinoma and unspecified subtypes of nasopharyngeal cancer, but not with non-keratinizing and undifferentiated subtypes. The risk of nasopharyngeal cancer (differentiated squamous-cell carcinoma and unspecified subtypes) increased significantly with increasing cumulative exposure (**Ptrend** = 0.033), duration of exposure (Ptrend = 0.014), and probability of exposure (possible, probable, or definite). The odds ratio (**OR**) was 1.6 (95% confidence interval [**CI**] = 1.0 to 2.8, 61 exposed cases) for possible, probable, or definite exposure, increasing to 2.1 (95% CI = 1.1 to 4.2, 27 exposed cases) for probable or definite exposure, and 13.3 (95% CI = 2.5 to 70, 10 exposed cases) for definite exposure.

"Other studies also found the highest risks of nasopharyngeal cancer for individuals with the highest formaldehyde exposure levels (assessed as cumulative exposure, exposure level, or exposure score) (Vaughan *et al*. 1986, Roush *et al*. 1987) and/or longest exposure durations (Vaughan *et al*. 1986, West *et al*. 1993 [after lagging exposures for 10 years]). Risks were also significantly elevated for individuals with longer time since first exposure (West *et al*. 1993) or who died at an older age (Roush *et al*. 1987); risk was increased fourfold for individuals who died after the age of 68 and were probably exposed to high levels of formaldehyde for at least 20 years before death. The associations between formaldehyde exposure and nasopharyngeal cancer remained after adjustment for or consideration of potential confounding by tobacco smoking (Vaughan *et al*. 1986, 2000, West *et al*. 1993, Hildesheim *et al*. 2001) or by exposure to wood dust (West *et al*. 1993, Vaughan *et al*. 2000, Hildesheim *et al*. 2001). Not all of the estimates of increased risk were statistically significant, and some studies (Armstrong *et al*. 2000, Li *et al*. 2006, Hauptmann *et al*. 2009) did not find an association between formaldehyde exposure and nasopharyngeal cancer. However, most of these studies were limited by small numbers of individuals exposed to formaldehyde. The overall consistency of the findings argues against their being attributable to chance.

"Excess mortality from nasopharyngeal cancer was found in the NCI cohort of industrial workers exposed to formaldehyde (standardized mortality ratio [**SMR**] = 2.10, 95% CI = 1.05 to 4.21). Relative risk increased with increasing cumulative exposure (Ptrend = 0.025 across exposed subjects), peak exposure (Ptrend <0.001), and average exposure (Ptrend = 0.066) (Hauptmann *et al*. 2004). Of the 7 exposed workers who died of nasopharyngeal cancer, all were in the highest peak-exposure category, and 6 were in the highest average-exposure category. Controlling for co-exposure to 11 potential occupational carcinogens and for plant did not alter the exposure-response relationships for nasopharyngeal cancer. Although the cohort included workers in 10 plants, most of the cases of nasopharyngeal

cancer occurred in workers in the plant with the largest numbers of workers in the highest formaldehyde exposure category; 46% of workers at Plant 1 were in the highest peak-exposure category, compared with 20.1% of workers in all other plants (Stewart *et al*. 1990, Marsh and Youk 2005). A nested case-control study of nasopharyngeal cancer among workers in Plant 1 found a significantly elevated risk for ever having worked in silversmithing jobs before or after employment at Plant 1; however, silversmithing was not correlated with formaldehyde exposure levels at this plant and therefore was not a confounding factor for formaldehyde exposure (Marsh *et al*. 2007).

"No excesses of nasopharyngeal cancer mortality were found in the other large cohort studies (Coggon *et al*. 2003, Pinkerton *et al*. 2004); however, the statistical power of these studies was inadequate to evaluate the risks of rare types of cancer."

Sinonasal cancer

"The evidence that formaldehyde exposure causes sinonasal cancer comes from consistent findings of increased risk in population-based case-control studies (Olsen *et al*. 1984, Olsen and Asnaes 1986, Hayes *et al*. 1986, Roush *et al*. 1987, Luce *et al*. 1993) and a pooled analysis of 12 case-control studies (Luce *et al*. 2002) that found an excess of sinonasal cancer. In most studies, estimates of increased risk were statistically significant for individuals ever exposed to formaldehyde, or with higher probabilities or levels of exposure (Olsen *et al*. 1984, Olsen and Asnaes 1986, Hayes *et al*. 1986, Luce *et al*. 1993, 2002).

"Elevated risks were observed for both adenocarcinoma and squamous-cell carcinoma; however, some studies suggested that adenocarcinoma was more strongly associated with formaldehyde exposure than was squamous-cell carcinoma (Luce *et al*. 1993, 2002). The pooled analysis (which included studies by Hayes *et al*. 1986, Vaughan *et al*. 1986, and Luce *et al*. 1993) was especially informative for evaluating sinonasal cancer, because it had greater statistical power for evaluating risks of rare cancers than did the individual studies, and it used an independent exposure analysis to assess cumulative exposure, rather than relying on the exposure estimates from the original studies. In the pooled analysis, the relative risk of adenocarcinoma increased with increasing cumulative exposure; the odds ratios for individuals with high cumulative exposure were 3.0 (95% CI = 1.5 to 5.7, 91 exposed cases) for men and 6.2 (95% CI = 2.0 to 19.7, 5 exposed cases) for women. Support for a positive exposure-response relationship also comes from a case-control study in France that found higher risks of sinonasal cancer (adenocarcinoma) among individuals with higher average exposure levels and earlier dates of first exposure (Luce *et al*. 1993) and from a case-control study in the Netherlands that found a significantly ($P < 0.05$) higher relative risk of all sino-nasal cancer or squamous-cell carcinoma among individuals with "high" exposure than those with "low" exposure (Hayes *et al*. 1986).

"Although co-exposure to wood dust is a potential confounding factor for sinonasal cancer, and specifically for adenocarcinoma, increased risk of sinonasal cancer associated with formaldehyde exposure has been found among individuals with little or no exposure to wood dust or after adjustment for wood-dust exposure (Olsen *et al*. 1984, Hayes *et al*. 1986, Olsen and Asnaes 1986). Some studies suggested that co-exposure to formaldehyde and wood dust had an interactive (synergistic) carcinogenic effect (Luce *et al*. 1993, 2002). Two case-control studies did not find an association between formaldehyde exposure and sinonasal cancer; however, one study included only 12 cases of sinonasal cancer in exposed individuals (Vaughan *et al*. 1986), and the other had methodological limitations (Pesch

et al. 2008). In the cohort studies of industrial workers (including studies of the large NCI, NIOSH, and British cohorts) and professional groups, the statistical power to detect an association between form-aldehyde exposure and sinonasal cancer was limited. Nonetheless, a statistically significant excess of sinonasal cancer incidence was found among Danish male workers exposed to formaldehyde and who were unlikely to have been exposed to wood dust (Hansen and Olsen 1995, 1996), and a nonsignificant excess of mortality from sinonasal cancer was found in the NCI cohort. No excess mortality from sinonasal cancer was found in the other cohort studies; however, the statistical power of these studies was inadequate to evaluate the risks of types of cancer."

Lymphohematopoietic cancer

"Evidence that demonstrates an association between formaldehyde exposure and combined lymphohematopoietic cancer is as follows: (1) in the NCI cohort of industrial workers, risk was significantly higher for the highest peak-exposure group than the lowest peak-exposure group, and a positive exposure-response relationship based on peak exposure was found (Beane Freeman *et al*. 2009), (2) increased risks were found in all of the cohort studies of professional groups (NTP 2010), and (3) a significant risk was reported (relative risk [RR] = 1.25, 95% CI = 1.12 to 1.39) in the meta-analysis by Zhang *et al*. (2009). In the NCI cohort study of industrial workers, the risks of Hodgkin lymphoma and multiple myeloma also were significantly higher among individuals with the highest peak exposure than those with the lowest peak exposure, and a positive exposure-response relationship was found for Hodgkin lymphoma (Beane Freeman *et al*. 2009). The other studies gave conflicting results for these two types of cancer. In the meta-analyses by Zhang *et al*. (2009), a significant association was found for multiple myeloma, but not for Hodgkin lymphoma. Because the evidence for these two types of cancer is mainly limited to the NCI cohort study, a causal association is not established.

"Increased risks for leukemia (all types combined) were found in all of the professional studies and some of the industrial cohort studies (NTP 2010). Among studies that evaluated subtypes of lymphohematopoietic cancer or leukemia, the strongest associations were observed for myeloid leukemia." (NTP RoC, 2016).

The IARC Monograph on formaldehyde summarised the mechanistic data for cancer of the nasopharynx and nasal sinuses:

"Mechanistic evidence supporting a causal relation between inhalation of formaldehyde and induction of cancer of the nasopharynx and nasal sinuses is based on the chemical reactivity of formaldehyde in producing **DNA**–protein crosslinks, and its genotoxicity *in vitro* and *in vivo*, including in the nasal cells of exposed humans. Computational fluid-dynamic models of formaldehyde in the nasal passages of rats, monkeys and humans have generally been accurate in predicting the area in the nose with the highest number of DNA–protein crosslinks (Georgieva *et al*., 2003). Local effects in the nasal passages, genotoxicity, and cell-proliferation rate appear to be the major determinants of nasal carcinogenicity after exposure to formaldehyde."

"The current data strongly indicate that genotoxicity plays an important role in the carcinogenicity of formaldehyde in nasal tissues in humans, and that cellular replication in response to formaldehyde-induced cytotoxicity promotes the carcinogenic response. Three possible mechanisms, all focused

around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (Reference cited in IARC, 2017).

The ANSES review of formaldehyde summarised the mechanistic data for leukaemia:

"Assumptions describing the leukaemogenic mode of action of formaldehyde have not yet been verified by experimental animal and/or *in vitro* studies. In fact, blood concentrations of formaldehyde increase only slightly or insignificantly after exogenous exposure to formaldehyde, even at high concentrations. In addition, the assumption that formaldehyde has cytotoxic action targeting bone marrow cells is questionable since formaldehyde is cytotoxic regardless of the cell type.

"Lastly, animal studies provide no evidence of leukaemia occurring at the formaldehyde exposure levels associated with the occurrence of nasal cancers. In fact, the incidence of leukaemia or lymphoma in animals increased only in the groups with the highest tested concentrations." (ANSES, 2018).

Animals

The ANSES review of formaldehyde summarised the potential for genotoxicity:

"Formaldehyde has shown *in vitro* genotoxicity at high concentrations in bacteria and mammalian cell genotoxic assays (IARC, 1997; Health Canada, 2001). The mutagenic potential of formaldehyde is reduced by adding an exogenous metabolic activation system, which suggests that formaldehyde itself is probably genotoxic (INRS, 2006). Formaldehyde also forms **DPX** crosslinks whose incomplete repair can lead to mutations (Barker *et al*., 2005) or clastogenic effects (ANSES, 2011).

"Regarding the genotoxic effects of formaldehyde away from the contact site, the results of the various studies undertaken in humans are conflicting and ambiguous. The European Chemicals Agency (**ECHA**) considered they could not be used to assess the mutagenic potential of formaldehyde. It recalls that, from a biological point of view, systemic effects are not expected since exposure to formaldehyde does not increase blood concentrations of formaldehyde (ECHA, 2012).

"In conclusion, there is insufficient evidence to confirm whether formaldehyde has systemic genotoxicity in humans. The results of micronucleus tests with circulating lymphocytes from various studies in workers exposed to formaldehyde indicate a correlation between the level and duration of exposure to formaldehyde and the occurrence of genetic instability in circulating lymphocytes in the form of micronuclei when the lymphocytes are cultured *ex vivo*. However, these tests were unable to identify whether the observed micronuclei were due to the effect of formaldehyde on lymphocytes circulating in the blood, which would be a marker of exposure to formaldehyde, or if they were caused by an effect on lymphoid progenitor cells located in bone marrow, which by accumulating mutations, may generate circulating lymphocytes with greater genetic instability. It therefore appears difficult to conclude with certainty as to the systemic genotoxic potential of formaldehyde, as the weight of evidence is considered average or low.

> "As stated above, it is very unlikely that formaldehyde can be distributed in gonadal cells after inhalation. The few studies available on germ cells suffer from methodological biases and could not be used." (References cited in ANSES, 2018).

The IARC Monograph on formaldehyde summarised the available data on carcinogenicity studies in animals after inhalation or dermal exposures:

> "In one inhalation study in B6C3F1 mice, formaldehyde marginally increased the incidence of squamous cell carcinomas of the nasal cavity in males. The incidence of lymphoma in females exposed to 14.3ppm (27/121) was also marginally increased (P = 0.06) when compared (pair-wise) with controls (19/121) (CIIT, 1981; Kerns *et al*., 1983a, b; Gibson, 1984).
>
> "In six studies (Swenberg *et al*., 1980; CIIT, 1981; Albert *et al*., 1982; Kerns *et al*., 1983a, b; Gibson, 1984; Sellakumar *et al*., 1985; Feron, *et al*., 1988; Woutersen *et al*., 1989; Monticello *et al*., 1996; Kamata *et al*., 1997) in different strains of rats (F344, Wistar, and Sprague-Dawley), there were treatment-related increases in tumours of the nasal cavity (primarily squamous-cell carcinomas but also squamous-cell papillomas, polypoid adenomas, carcinomas, rhabdomyosarcomas, adenocarcinomas, and mixed/combined tumours). In one study (CIIT, 1981), the incidences of undifferentiated leukaemia [Fischer rat leukaemia, as indicated in the report] were 12/120 (control), 17/120 (2ppm), 16/120 (5.6ppm) and 7/120 (14.3ppm) in females; there was a marked decrease in survival in the animals exposed to the high dose. Based on a survival-adjusted analysis, the incidence of leukaemia in females exposed to 14.3ppm was increased compared with controls (P = 0.0056; Tarone-extension of the Cox test; level of significance, P <0.0167). [The Working Group noted that this type of leukaemia is a very common, spontaneously occurring neoplasm in the F344 rat strain]."
>
> "In one study in male and female hairless Oslo mice, topical application of 10% formaldehyde in water reduced the latency of 7,12-dimethylbenz[a] anthracene-induced skin tumours (Iversen, 1986)." (References cited in IARC, 2012).

4.3 Absorption, distribution, metabolism and excretion

The ANSES review of formaldehyde summarised the toxicokinetics:

> "Formaldehyde is an endogenous compound formed naturally by the body through amino acid catabolism. Its physiological blood concentration is around 100**µmol.L-1** (BfR, 2006b). Whether in animals or humans and regardless of the route of exposure, the retention of formaldehyde is limited to the site of first contact in the body, due to its reactivity with biological macromolecules, which limits its systemic availability (ATSDR, 1999). Several studies have shown no differences between blood levels of formaldehyde before and after respiratory exposure to formaldehyde, in humans and rats (Heck *et al*., 1985; Casanova *et al*., 1988).
>
> "Formaldehyde is rapidly metabolised into formate and then CO2 by several enzymes, the most important being **NAD**+-dependent formaldehyde dehydrogenase (FDH). Formaldehyde reacts rapidly with glutathione (GSH) to form hydroxymethylglutathione (GS-CH2OH), which is subsequently oxidised in the presence of FDH into S-formylglutathione (G-S-CHO).

The hydrolysis of this compound releases glutathione and a formate ion (HCOO-), which is either eliminated in the urine or oxidised into CO2 and eliminated primarily in the lungs (ATSDR 1999; BfR, 2006b). This mechanism is saturable: the sharp increase in toxicity in rats at concentrations above 6ppm can be interpreted as being due to saturation of FDH or depletion of GSH (BfR, 2006).

"When it is not metabolised, because of its high reactivity with the functional groups of the molecules, formaldehyde may bind covalently with the nucleophilic sites of proteins, small- and medium-sized molecules, and DNA (ATSDR, 1999; National Institute for Working Life, 2003). This route is responsible for the formation of DNA-protein cross-links (DPXs) in the nasal mucosa, playing a crucial role in the carcinogenic mode of action of formaldehyde in the nasopharynx. No increase in DPXs related to exogenous formaldehyde was observed in bone marrow or away from the absorption site (Heck and Casanova, 2004; Lu *et al*., 2010; Golden, 2011).

"Expired air is the primary route of elimination, with around 40% of formaldehyde eliminated in the form of carbon dioxide. Regardless of the concentration of formaldehyde to which animals are exposed, the rates of elimination through the three routes are of the same order of magnitude (Heck *et al*., 1983; IARC, 2006)." (References cited in ANSES, 2018).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows the formaldehyde exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia	1	1.2	2	2.5
Austria	0.3	0.37	0.6[1]	0.74[1]
Belgium			0.3[2]	0.38[2]
Canada – Ontario			1 1.5[1]	
Canada – Québec			2[1]	3[1]
Denmark	0.3	0.4	0.3	0.4
Finland	0.3	0.37	1[1]	1.2[1]
France	0.5		1	
Germany – **AGS**	0.3	0.37	0.62	0.74[2]
Germany – **DFG**	0.3	0.37	0.6[2,3]	0.74[2,3]
Hungary		0.6		0.6
Ireland	2	2.5	2[4]	2.5[4]
Israel	0.2	0.24	0.3[1]	0.37[1]
Japan – **MHLW**	0.1			
Japan – **JSOH**	0.1	0.12		
Latvia		0.5		
New Zealand	0.5[5] 0.33[6]			
People's Republic of China				0.5[1]
Poland		0.5		1
Romania	1	1.2	2[2]	3[2]
Singapore			0.3	0.37
South Korea	0.5	0.75	1	1.5
Spain			0.3	0.37
Sweden	0.3	0.37	0.6[2]	0.74[2]
Switzerland	0.3	0.37	0.6	0.74
The Netherlands		0.15		0.5
USA – NIOSH	0.016		0.1[1]	
USA – **OSHA**	0.75		2	
UK	2	2.5	2	2.5

TABLE 3: Exposure standards for formaldehyde from around the world

[1] **Ceiling limit value**.
[2] 15 minutes average value.
[3] A momentary value of 1ml/m³ (1.2mg/m³) should not be exceeded.
[4] 15 minutes reference period.
[5] 8-hour shift.
[6] 12-hour shift.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on formaldehyde were ANSES, SCOEL, ACGIH® and Safe Work Australia.

5.2 ANSES

The ANSES review of formaldehyde endorsed the OELs proposed by the OEL Committee and the Occupational **DNEL**s proposed by the **REACH** Committee (ANSES, 2018).

The OEL Committee recommended an 8-hour OEL of 369µg/m³ [0.3ppm] rounded to 350µg/m³ [0.3ppm], based on a NOAEC of 0.3ppm for sensory irritation from the study by Lang *et al*. (2008 cited in ANSES, 2018); and, a 15-minute **STEL** of 738µg/m³ [0.6ppm] rounded to 700µg/m³ [0.6ppm], based on a NOAEC of 0.6ppm for eye irritation from the study by Lang *et al*. (2008 cited in ANSES, 2018).

The ANSES review of formaldehyde summarized the selection of the chronic critical effect:

> "The selected critical effect of chronic exposure to formaldehyde was nasopharyngeal cancer. It is the best described carcinogenic effect of formaldehyde, for which a causal relationship has been well established based on numerous human, animal and mechanistic data. The development of nasopharyngeal cancer is linked to repeated and prolonged changes in the nasal epithelium, and therefore to sufficiently high and prolonged exposure first causing irritation. The data on the mode of action enable a threshold dose-response relationship to be determined, with a series of key events leading to the formation of nasopharyngeal tumours of which the first is eye and nose irritation.
>
> "Regarding leukaemia, the level of evidence is considered sufficient by the IARC for exposure to formaldehyde at high concentrations at which nasopharyngeal cancer is also observed. Even so, the causal relationship could not be confirmed due to confounding biases and uncertainties regarding the characterisation of exposure in particular. Furthermore, assumptions describing the mode of action have not yet been verified by experimental animal and/or *in vitro* studies. Animal studies provide no evidence of leukaemia at the formaldehyde exposure levels associated with the occurrence of nasal cancers. Experimental studies conducted orally lead to the same conclusion. The carcinogenic effects on the nasopharynx were therefore the most sensitive critical effect of chronic exposure to formaldehyde in humans.
>
> "As indicated above, eye irritation is observed at formaldehyde concentrations below those associated with nasal and respiratory irritation. Moreover, these effects are generally reversible after the end of exposure in human controlled exposure studies. Eye irritation is therefore the first key event and is a precursor of more severe irreversible effects such as nasopharyngeal carcinogenic effects of formaldehyde. Its selection as the critical effect for the establishment of a chronic value appeared as the most conservative for preventing the occurrence of long-term effects.
>
> "In order to protect against the occurrence of nasopharyngeal cancers, the selected effect was therefore eye irritation." (ANSES, 2018)

The ANSES review of formaldehyde noted that for chronic exposures the selected NOAEC of 369µg/m³ [0.3ppm] was based on the formaldehyde exposure level of 369µg/m³ + 4 x 738µg/m³ [0.3 + 4 x 0.6ppm], and that:

> "the data show that no particular susceptibility to formaldehyde was noted. In addition, the selected critical effect (sensory irritation) appears at lower concentrations than those producing cellular irritation. Considering the carcinogenic mode of action of formaldehyde, this cellular irritation is a precursor of events that can lead to the occurrence of nasopharyngeal cancer.
>
> "In view of this precursor effect, the low inter-individual variability and the concordance of the numerous studies on formaldehyde, it was not deemed necessary to apply an uncertainty factor.
>
> "As the duration of exposure in the key study was four hours, the relevance of applying a temporal adjustment to match the duration of a working day (eight hours) was discussed. However, as stated above, the irritation phenomena are concentration-dependent rather than time-dependent effects (Belkebir *et al*., 2011). This is also confirmed by studies with longer exposure durations in which the effects are observed at comparable doses. A temporal adjustment was therefore not considered necessary." (ANSES, 2018)

For acute exposures the selected NOAEC of 738µg/m³ [0.6ppm] was based on the formaldehyde exposure level of 369µg/m³ + 4 x 738µg/m³ [0.3 + 4 x 0.6ppm], and that:

> "The application of an uncertainty factor was discussed for this value considering the very likely inter-individual variability in eye irritation and especially ocular dryness. Nevertheless, in the workplace, this had already been taken into account by the many available studies on formaldehyde (total number of exposed subjects in the two key studies and the epidemiological studies). As no other uncertainty factor was deemed relevant, the decision was made not to apply an uncertainty factor." (ANSES, 2018)

The ANSES review also noted that the OEL Committee recommended that **"skin"** and **"noise"** notations were not required:

> "Due to the very high reactivity of formaldehyde at the contact site, penetration by the dermal route seems very low, and the contribution of this route to a possible systemic effect (not currently demonstrated for formaldehyde) seems negligible. The "skin" notation is therefore not selected for formaldehyde."
>
> "None of the available studies suggest an ototoxic effect of formaldehyde. Accordingly, the "noise" notation is not assigned." (ANSES, 2018)

5.3 SCOEL

The SCOEL review of formaldehyde [FA] recommended for occupational exposures to formaldehyde a Limit Value of 0.3ppm [8-hour TWA] with a STEL of 0.6ppm (SCOEL, 2017).

The rationale for their conclusions was:

> "The primary aim of an Occupational Exposure Limit (OEL) for FA is to avoid upper respiratory tract cancer as has been observed in rodents, especially in rats at exposure concentration of ≥6ppm. In addition an OEL should also protect against undue annoyance for the worker population. Tumour induction

by FA is driven by sustained cytotoxicity and cell proliferation while genetic changes are secondary (McGregor *et al*., 2006). Therefore for FA a threshold can be established for concentrations not leading to such sustained cell proliferation and histopathological alterations. A NOAEC has been established in the sensitive rat for histopathological alterations at 1ppm and for regenerative cell proliferation based on the large experimental database (Gelbke *et al*., 2014). Under these considerations FA is considered a group C carcinogen (genotoxic carcinogens for which a practical threshold is supported; Bolt and Huici-Montagud, 2008; SCOEL, 2013). This classification corresponds closely to that of the German MAK commission (DFG, 2015) as a group 4 carcinogen.

"Data pivotal for the derivation of an OEL, namely the NOAEC for sustained cytotoxic irritation, are only available for experimental animals, but not for humans for ethical reasons. The rat is a poor and most probably over-sensitive model in this respect due to its different respiratory physiology while the monkey exhibits many similarities to humans (DeSesso, 1993). There are clear indications that the monkey is less sensitive than the rat if FA-DNA adducts (Moeller *et al*, 2011, Swenberg *et al*, 2011) or DNA-protein-crosslink (DPX) formation (Casanova *et al*, 1991) are taken as indicator for target tissue exposure. Humans are likely to be even less sensitive than monkeys (Casanova *et al*, 1991).

"On the other hand, there is a solid database for humans (comprising in total more than 400 volunteers) for sensory irritation of FA on the eye, a very sensitive parameter (DECOS 2003, Nordic Expert Group 2003). It is generally considered that avoidance of sensory irritation of the eye and the upper respiratory tract would automatically imply a safety margin to also avoid cytotoxic irritation-induced local cell proliferation as a first step to tumour induction. Derivation of an OEL based on sensory eye irritation in humans inherently provides a broad margin of safety in comparison to the induction of upper respiratory tract tumours in rats for the following reasons:

- Sensory irritation occurs at lower concentrations than cytotoxic irritation (Brüning *et al*, 2014).
- Due to confounding factors, like personality traits or odour, subjective symptoms of irritation (as generally only measured in pre-2000 studies) tend to overestimate sensory irritation as measured by objective parameters.
- In humans sensory irritation to the eyes occurs at lower concentrations than sensory irritation to the respiratory tract, the potential target for FA induced tumours (Brüning *et al*, 2014).
- Due to the differences in respiratory physiology rats are more sensitive than monkeys and monkeys probably more sensitive than humans with regard to DPX formation (Casanova *et al*, 1991).
- The amount of DNA adducts is higher in rats than in monkeys at comparable exposure concentrations and especially also the ratio of exogenous/endogenous adducts (Swenberg *et al*, 2011).
- One important aspect has to be taken into consideration for all extrapolations from high dose experimental data to low human exposures, namely the steep upward bent dose response curve, being most pronounced at concentrations ≥2ppm, for all decisive parameters, like tumour incidences (Kerns *et al*, 1983; Monticello *et al*., 1997), cell proliferation (Monticello *et al*, 1997), DPX formation (Casanova *et al*., 1991) and **dG** adducts (Lu *et al*., 2011). Also cell proliferation (as measured by PWULLI – Population-Weighted Unit Length Labelling Index) vs. %-tumour rate shows a steep upward bent relationship (Monticello and Morgan, 1997).
- This dose response relationship has also been found by *in vitro* genotoxicity studies (Speit *et al*, 2007).

"Although it has to be acknowledged that these points cannot be quantitatively agglomerated to a numerical uncertainty factor (in the sense of SCOEL, 2013), SCOEL will primarily base its considerations on objective parameters for sensory irritation obtained by human volunteer studies.

"With the availability of two volunteer exposure studies complementing each other and not only measuring subjective reportings but also objective signs of eye and upper respiratory tract irritation (Lang *et al*., 2008; Mueller *et al*., 2013), an OEL can now be based on objective parameters not potentially biased by personality traits like anxiety or expectations. Such factors will not play a role for subjects used to work with FA. A synopsis of both studies leads to a NOAEC for objective parameters of sensory irritation of 0.7ppm or 0.4ppm with peaks of 0.8ppm. Both studies applied slightly different concentration regimes. Exposures with 4 superimposed peaks being most relevant for derivation of an OEL with STEL were 0.3ppm + peaks of 0.6ppm and 0.5ppm + peaks of 1ppm in the Lang study, and in that of Mueller 0.3ppm + peaks of 0.6ppm and 0.4ppm + peaks of 0.8ppm. Objective signs of irritation were only observed at 0.5ppm + peaks of 1ppm. Because 0.3ppm + peaks of 0.6ppm was a consistent NOAEC in both of these investigations this exposure regime is proposed as the basis for an OEL with STEL. This NOAEC based on 62 volunteers (41 in the Mueller study and 21 in the Lang study) is sufficiently robust for the derivation of a Limit Value. No further uncertainty factor for possible human inter-individual variations is necessary, especially as low interindividual variation is also confirmed by the older studies reviewed by Paustenbach *et al*. (1997). Thus for high quality volunteer studies, Brüning *et al*. (2014) recently concluded that an OEL may be based on the NOAEC without an additional safety factor. Also, these authors propose an interspecies extrapolation factor of 3 for extrapolating animal data to humans concerning local irritation effects, but this may be reduced to 2 because of existing modellings of the airway physiology and FA deposition of rats and humans. Starting from the NOAEC of 1ppm in rats this would lead to 0.5 or 0.3ppm similar to the NOAECs found in human volunteers.

"In conclusion, SCOEL recommends a Limit Value of 0.3ppm (8h TWA) with a STEL of 0.6ppm corresponding to the NOAECs for objective signs of sensory irritation in human volunteer studies. An additional uncertainty factor according to SCOEL (2013) is not used as no corresponding factors need to be covered in addition and since the critical effect has been studied with essentially the same results in many investigations, including the older ones concentrating on subjective symptoms.

"This 8h TWA is further supported by risk extrapolations from experimental animals to humans (Conolly *et al*., 2004; Andersen *et al*., 2010; Starr and Swenberg, 2013).

"Finally it needs to be addressed whether the recommended Limit Value of 0.3ppm (8h TWA) with 4 peaks of 0.6ppm (STEL) will also protect from irritation and undue annoyance [in the sense of "nuisance" according to SCOEL (2013)]. No subjective symptoms of irritation were observed by Mueller *et al*. (2013) up to the highest exposure. In contrast, in the study of Lang *et al*. (2008) subjective symptoms were already reported at concentrations as low as 0.3ppm. But when negative affectivity was used as covariate the only effect level was 0.5ppm + peaks at 1ppm as for objective signs of irritation. As negative affectivity will not play a decisive role at the workplace, these findings for subjective symptoms of irritation have to be considered as grade (1) or at most between grade (1) and (2) (SCOEL, 2013; chapter 3.1).

> "Odour perception was reported in both studies. This was statistically significantly increased in Lang *et al*. (2008) at ≥0.3ppm but the odour of 12–16ppm ethyl acetate was perceived stronger than that at 0.5ppm and similar to that at 0.5ppm + peaks of 1ppm FA. Similar results were reported for annoyance. In the study of Mueller *et al*. (2013) again significant differences were noted for olfactory symptoms without a concentration effect relationship and especially for the "perception of impure air", most pronounced in the group of hypersensitive persons against CO_2 nasal irritation. Olfactory symptoms were dominated by "perception of impure air". For the complaint "perception of impure air" a statistically significant increase was already noted at 0ppm (pre- vs. end of exposure) in hypersensitive persons. Therefore this item cannot be ascribed to FA only. Because a statistically significant difference in symptom scores between FA exposures and control conditions was missing, the authors concluded that the increase in olfactory symptoms is mainly induced by displeasing ambient smell and the situational and climatic conditions in the exposure chamber. Again FA related olfactory symptoms and "perception of impure air" may at most reach a grading between (1) and (2) according to SCOEL (2013; chapter 3.1).
>
> "In conclusion, a Limit Value of 0.3ppm with a STEL of 0.6ppm will also protect from "nuisance" at the workplace caused by subjective symptoms of irritation and odour.
>
> "It is noted that that the Limit Value of 0.3ppm with a STEL of 0.6ppm deviates from the "preferred value" concept of SCOEL (2013) using decimals of integers 1, 2, or 5ppm. This deviation is scientifically justified as the derivation of the Limit Value is based on an exceptionally broad database of actual NOAECs from human volunteer studies.
>
> "As explained in chapter 7.9, a possible induction of myeloid leukaemia by FA in humans would require that FA acts systemically and thereby reaches the bone marrow, which is the target tissue for leukaemia. Such a systemic toxicity is not possible within the exposure range where the external FA dose does not change the internal physiological level of FA, that is, less at exposures up to 0.4ppm. This means that the human physiological homeostasis of endogenous FA is not challenged within the range of the proposed OEL, and consequently, that no systemic effects can be expected under such exposure conditions." (References cited in SCOEL, 2017).

The SCOEL review noted that: as a result of the predominantly local effects of formaldehyde, a "skin" notation was not required; formaldehyde was a well-known contact allergen to the skin (skin sensitiser), therefore a sensitisation (Dermal) notation was required; but against the background of widespread use, respiratory sensitisation had only been reported occasionally, and therefore the designation as respiratory sensitizer was not warranted. The SCOEL review also noted that formaldehyde does not induce or exacerbate asthma in asthmatics at formaldehyde concentrations below 1ppm (SCOEL, 2017).

5.4 ACGIH®

The ACGIH® review of formaldehyde concluded that a **TLV-TWA** of 0.1ppm [0.12mg/m^3] with a **TLV-STEL** of 0.3ppm [0.37mg/m^3] were recommended for occupational exposure to formaldehyde to minimise the potential for sensory irritation [chiefly of the eye and upper respiratory tract] (ACGIH®, 2017).

The rationale for their conclusion was:

> "The lowest-observed-adverse-effect levels (**LOAEL**s) for eye and upper respiratory tract irritation from human experimental studies (Lang *et al*., 2008) and cross-sectional studies of workers (Alexandersson and Hedenstierna, 1988) involved both continuous and peak exposures. Therefore, a combination of a TWA and a STEL are recommended. Human (Beane Reeman *et al*., 2013) and animal (Kerns *et al*., 1983; Monticello *et al*., 1996) studies have indicated nonlinear dose-response relationships for the risk of squamous cell nasal cancer. The most likely mechanism of cancer induction involves cytotoxicity, cell proliferation, and/or genotoxicity. By minimizing repeated irritation to the respiratory tract and also minimizing the potential for a genotoxic outcome, the TLV should protect against the risk of upper respiratory tract cancer.
>
> "The LOAEL for objective measurements of irritation (blinking rate and conjunctival redness) from an experimental human chamber study of a group of healthy volunteers exposed for 4-hour sessions on 10 consecutive working days was 0.5ppm formaldehyde, with short-term peak exposures of 1.0ppm (Lang *et al*., 2008). Supporting evidence from another controlled human experimental study comes from Andersen and Molhave (1983). Several cross-sectional studies have been done on workers having occupational exposure to formaldehyde. Alexandersson and Hedenstierna (1988) reported eye and respiratory tract irritation in lacquer workers exposed at a mean formaldehyde air concentration of 0.3ppm (8-hr TWA) with a peak of 0.6ppm. Horvath *et al*. (1988) found a LOAEL of 0.4ppm (8-hr TWA) for nasal irritation among workers in a particle board and molded products factory who, in addition to formaldehyde exposures, also had mean particulate exposures of 0.38mg/m^3. Holness and Nethercott (1989) reported a significant excess risk of nose and eye irritation among embalmers with a mean formaldehyde exposure of 0.36ppm, compared to a control group with a mean exposure of 0.02ppm. A study of workers in factories processing particle boards or laminates, with long-term exposure to 0.08–0.90ppm and peaks up to 4ppm formaldehyde, found a significant excess of histopathological changes in nasal mucosa (loss of cilia, goblet cell hyperplasia, squamous metaplasia, and mild dysplasia) compared to a nonexposed group of workers (Edling *et al*., 1988). There was no difference in histologic changes between the group exposed only to formaldehyde and the group exposed to wood dust and formaldehyde.
>
> "The A1, Confirmed Human Carcinogen, notation is recommended, based on the following:
>
> 1. Elevated risk of nasopharyngeal cancer from several epidemiologic studies (Beane Freeman *et al*., 2013; Hildesheim *et al*., 2001; Vaughan *et al*., 1986a, b, 2000; West *et al*., 1993). All of the studies were considered to be strong or moderately strong in study quality by the National Academy of Sciences (2014). The evidence that smoking could affect the results of these studies is inconsistent and only modest in strength (Roush *et al*., 1987; Beane Freeman *et al*., 2013).
> 2. Reports of short-term (Feron *et al*., 1988) and chronic animal inhalation studies in which exposed rats (Kerns, *et al*., 1983; Rusch, *et al*., 1983; Sellakumar *et al*., 1985, Monticello *et al*., 1986) and mice (Kerns *et al*., 1983) displayed tumorigenic responses that included squamous metaplasia, papillary hyperplasia, and squamous cell carcinomas of the nasal cavity.
> 3. Concordance of anatomic site (upper respiratory tract) and histologic cell type (squamous-cell carcinoma) in human epidemiology and animal experimental studies of nasopharyngeal cancer.

4. A significant increase in cell proliferation in the nasal epithelium of rats and mice was seen 18 hours after a single 6-hour exposure to 15ppm formaldehyde (Chang *et al*., 1983). The result in rats was confirmed by Speit *et al*. (2011) who found an increase in cell proliferation in rats exposed at 6ppm or higher for 4 weeks. Increased cell proliferation was also seen in rhesus monkeys exposed to 6ppm for 6 weeks (Monticello *et al*., 1989).
5. Evidence of genotoxicity in rodents, (Casanova *et al*., 1989), rhesus monkeys (Casanova *et al*., 1991), and humans (Costa *et al*., 2011; Bono *et al*., 2010; Viegas *et al*., 2010) exposed to formaldehyde.

"Although it is not possible to precisely measure lifetime exposure in occupational epidemiology studies, the largest cohort study (Beane Freeman *et al*., 2013) found a significant increase in deaths from nasopharyngeal cancer only in the subset of workers whose average exposure was greater than or equal to 1ppm. The no-observed-adverse-effect level (**NOAEL**) for squamous cell nasal cancer in a rat inhalation study is 2ppm (Kerns et a., 1983; Monticello *et al*., 1996). The NOAEL for nasal squamous cell metaplasia in monkeys exposed continuously for 26 weeks is 1ppm (Rusch *et al*., 1983).

"Computer modelling projections, based on the mode-of-action, production of DNA-protein cross-links, and tissue dosimetry (combining animals and human data), suggest that human cancer risks of long-term exposure to formaldehyde may be negligible at exposures below the recommended TLV-TWA of 0.1ppm (Kimbell *et al*., 2001; Oerton *et al*., 2001; Conolly *et al*., 2004; Swenberg *et al*., 2011; Starr and Swenberg, 2013, 2016).

"Based on the reports of allergenic reactions/sensitization following occupational and nonoccupational dermal exposures to formaldehyde, a **DSEN** notation is assigned. There are numerous reports of dermal allergic reaction or sensitization associated with exposure to formaldehyde and products containing formaldehyde (U.S. ATSDR, 1997; U.S. NIOSH, 1997a; Hendrick and Lane, 1977; Porter, 1975; Schachter *et al*., 1986; Imbus, 1985; Maurice *et al*., 1986; Berrins *et al*., 1964; O'Quinn and Kennedy, 1965; Uehara, 1978; Peck and Palitz, 1956; Glass, 1961; Hendrick *et al*., 1982; Bardana and Andrach, 1983; Arrandale *et al*., 2012; Perrenoud *et al*., 1994; Dearman *et al*., 1999; de Jong *et al*., 2009; Matsunaga *et al*., 2008).

"For respiratory sensitization the situation is more complex. Formaldehyde seems capable of causing asthma, a condition sometimes (but not always) associated with sensitization; therefore, and **RSEN** is assigned to highlight the potential for formaldehyde to cause occupational asthma. The primary evidence for formaldehyde as a respiratory sensitizer comes from a registry study of suspected cases of formaldehyde-induced occupational asthma referred to the Finnish Institute of Occupational Health (Nordman *et al*., 1985). Of 230 patients referred for evaluation, 12 were considered to be sensitized to formaldehyde, based on medical and occupational history and on specific bronchial provocation tests. The authors concluded that respiratory sensitization to formaldehyde is a real, although rare, event. In addition, there is supportive evidence from human case reports (Hendrick and Lane, 1997; Porter, 1975; Kim *et al*., 2001; Vandenplas *et al*., 2004) and from one follow-up study (Hendrick *et al*., 1982). Most of these case reports describe cases of asthma, rather than classical IgE-mediated sensitization. There is also suggestive evidence in humans that chronic exposure as low as 0.2ppm may activate the immune system, increasing susceptibility to respiratory hypersensitivity (Aydin *et al*., 2013)." (References cited in ACGIH®, 2017).

5.5 Safe Work Australia

Safe Work Australia proposed an 8-h TWA of 0.1ppm to protect for irritation of the eyes and upper respiratory tract and subsequently nasal cancer in exposed workers, and a STEL of 0.3ppm to protect for significant sensory irritation and subsequent nasal pathologies in exposed workers.

In their review, they say, "Effects from inhalation exposure to formaldehyde are primarily localised, manifesting as sensory irritation and cellular changes that may lead to cancer. The LOAEL for irritation following inhalation identified in humans are reported at 0.25 and 0.3ppm (ACGIH, 2018; HCOTN, 2003). Evidence in humans suggests that the prevention of irritation effects will protect against nasal cancers with results of a 40 year study indicating that exposure to 0.3ppm formaldehyde for 40 years produces very low additional cancer risks (DFG, 2000). This is supported by evidence in animals with a NOAEL for nasal cancer in rats reported at 2ppm and 1ppm for nasal effects in rats and monkeys, respectively (ACGIH 2018; SCOEL, 2017). Consequently, the recommended TWA of 0.1ppm is considered sufficient to protect against sensory irritation and therefore nasal cancer in all workers.

"Data from human studies indicate short term exposure to concentrations of approximately 1ppm results in slight eye irritation (ACGIH, 2018; HCOTN, 2003). Therefore, the recommended STEL of 0.3ppm is considered protective." (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne formaldehyde

A common method to measure formaldehyde exposure is using NIOSH Method 2016, Issue 2 (NIOSH, 2003).

Using this method an air sample of 1 to 15 litres is collected onto a sampling train consisting of a silica gel coated solid sorbent tube coated with 2,4-dinitrophenylhydrazine, with the sampling train set at a flow rate of 0.03 to 1.5 litres per minute. Alternatively a UMEX100 Passive Sampler treated with 2,4-dinitrophenylhydrazine can be used. Following extraction of the analyte using acetonitrile, the sample is analysed using high performance liquid chromatography with ultraviolet detection.

This method can achieve a detection limit of 0.07µg per sample. This would allow quantitation of samples at an airborne concentration of 0.004ppm after 8 hours or 15 minutes duration.

There are real-time measurement methods available to measure peak exposures of formaldehyde.

7.0
Discussion

WorkSafe's WES for formaldehyde has been unchanged since adoption in 2010.

The toxicological database reviewed above indicates that formaldehyde is locally toxic to humans, causing irritation to the skin, eye and mucous membranes, dermal sensitisation, and nasopharyngeal and nasal cancer; and locally toxic to laboratory species causing irritation to the skin, eyes and respiratory tract, and nasal tumours in rodents.

Based on the aforementioned documentation, informed by the conclusions of the ANSES, SCOEL, ACGIH® and Safe Work Australia reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA for formaldehyde of 0.5ppm [8-hour shift], 0.33ppm [12-hour shift] with a WES-Ceiling value of 1ppm to be inadequate to manage health risks from possible workplace exposure:

- Formaldehyde is genotoxic, including inducing micronuclei in nasal and oral mucosa cells, and DNA-protein cross-links in circulating white blood cells in humans after inhalation exposures (IARC, 2012).
- Formaldehyde has the potential to induce nasopharyngeal and nasal cancers (and possibly leukaemias) in exposed workers (IARC, 2012).
- Mechanistic evidence is biologically plausible for the induction of nasopharyngeal and nasal cancers by formaldehyde inhalation exposure, via cytotoxicity promoting cellular replication in genetically compromised target cells (IARC, 2012).
- The ANSES [2018], SCOEL [2017] and ACGIH® [2017] reviews all propose OELs or TLVs derived from LOAECs for sensory irritation endpoints from human studies, as sensory irritation is a more sensitive endpoint than cellular irritation, the critical triggering effect in the development of nasopharyngeal and nasal cancers (ANSES, 2018; SCOEL, 2017; ACGIH®, 2017).
- The ANSES [2018] review noted that the OEL and REACH Committees used data from Lang *et al*. (2008): NOAEC = 369µg/m^3 [0.3ppm], LOAEC = 615µg/m^3 [0.5ppm] with four 1230µg/m^3 [1.0ppm] peaks, without Uncertainty Factors.
- The SCOEL [2017] review used Lang *et al*. (2008) and Mueller *et al*. (2013) data: NOAEC = 0.3ppm for their 8-hour TWA of 0.3ppm, without Uncertainty Factors.
- The ACGIH® [2017] review used Lang *et al*. (2008) and other data: LOAEC = 0.5ppm for their TLV-TWA = 0.1ppm.
- The proposed WES-TWA of 0.1ppm for formaldehyde is set to be protective against all non-carcinogenic and non-genotoxic endpoints, based on NOAECs/LOAECs for sensory irritation in humans as the most sensitive marker for toxicity.
- The proposed WES-STEL of 0.3ppm for formaldehyde is set to be protective against acute eye or respiratory tract irritation. Duration [time-concentration] and peak concentration of exposure appear to be significant in the development of nasopharyngeal and nasal cancers in exposed workers, so that a WES-STEL or WES-Ceiling is required (ACGIH®, 2017).

- Skin penetration resulting in systemic toxicity is unlikely to occur in workers exposed to formaldehyde, due to the substance's high reactivity, unless the extent of exposure results in severe skin lesions [formaldehyde is classified as corrosive to skin and eyes] (NIOSH, 2011; ANSES, 2018). A ***skin*** *notation* is not justified.
- Based on human experience, formaldehyde is a dermal sensitiser (NIOSH, 2011). Allergic sensitisation is considered an irreversible change (**OECD**, 2012). A ***dsen*** *notation* is recommended.
- The evidence that formaldehyde is a respiratory sensitiser in exposed humans is not clear-cut. However, formaldehyde inhalation exposure has been linked to occupational asthma (ACGIH®, 2017). The ANSES [2018] and SCOEL [2017] reviews did not propose notations for respiratory sensitisation, while the ACGIH® [2017] review recommended only a DSEN notation. A ***rsen*** *notation* is not proposed.
- Threshold levels exist for allergic sensitisation by allergenic substances (OECD, 2012). However, any threshold level for the initiation of allergic sensitisation by allergenic substances may not be protective once an individual has become sensitised, and cross-sensitivity may occur with other related substances.

8.0
Recommendations

WorkSafe considers its current WES-TWA of 0.5ppm [8-hour shift], 0.33ppm [12-hour shift] with a WES-Ceiling value of 1ppm for formaldehyde to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for formaldehyde of 0.1ppm
2. remove the WES-TWA for formaldehyde of 0.33ppm [12-hour shift]
3. adopt a WES-STEL for formaldehyde of 0.3ppm
4. remove the WES-Ceiling for formaldehyde of 1ppm, and
5. adopt a *dsen* notation for formaldehyde.

Noting that the proposed WES-TWA of 0.1ppm [8-hour shift] and WES-STEL of 0.3ppm for formaldehyde may not eliminate all risk, due to the genotoxic and dermal sensitising potential of formaldehyde, so exposures should be minimised, particularly for individuals already sensitised to formaldehyde.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
AGS	Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
ANSES	Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail. The National Social Security Administration is a decentralized Argentine Government social insurance agency managed under the aegis of the Ministry of Labor and Social Security.
CI	Confidence Interval.
Ceiling or Ceiling Limit Value	Ceiling Limit Value – absolute exposure limit that should not be exceeded at any time.
DECOS	Dutch Expert Committee on Occupational Standards. A committee of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
dG	Deoxyguanosine.
DNA	Deoxyribonucleic acid.
DNEL	Derived No Effect Level.
DPX	DNA-protein cross-links.
dsen	A substance that can 'sensitise' the skin, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
DSEN	A notation indicating the substance is a dermal sensitiser. DSEN is used in place of SEN when specific evidence of sensitisation by the dermal route is confirmed by human or animal data. An ACGIH® term.
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
FA	Formaldehyde.
GPMT	Guinea pig maximization test.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	The International Agency for Research on Cancer – an agency of the World Health Organisation.
IgE	Immunoglobulin E.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
IPCS	International Programme on Chemical Safety – a World Health Organisation Programme.
JSOH	Japan Society for Occupational Health.
LLNA	Local lymph node assays.
LOAEL	Lowest Observed Adverse Effect Level.

TERM	MEANING
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
MHLW	Japanese Ministry of Health, Labour and Welfare.
µg/m^3 or µg.m^{-3}	Micrograms of substance per cubic metre of air.
µmol/L or µmol.L^{-1}	Micromole of substance per litre of the matrix.
mg	Milligram or one thousandth of a gram.
mg/m^3	Milligrams of substance per cubic metre of air.
NAD	Nicotinamide Adenine Dinucleotide – a cofactor found in all living cells involved in redox reactions, carrying electrons from one reaction to another.
NCI	US National Cancer Institute.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NOAEC	No Observed Adverse Effect Concentration.
NOAEL	No Observed Adverse Effect Level.
"noise"	A notation indicating the potential for ototoxic effects [damage to the inner ear].
NTP	National Toxicology Program, US Department of Health and Human Services.
Odds Ratio; OR	An odds ratio is a measure of association between an exposure and an outcome – the odds that an outcome will occur given a particular exposure, compared to the odds of the exposure occurring in the absence of that exposure.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Level (equivalent to a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
ppm	Parts of vapour or gas per million parts of air.
Ptrend	A statistical parameter for a test that calculates the probability of a trend within two variables in a postulated monotonic relationship (where the variables tend to move in the same relative direction, but not necessarily at a constant rate; that is, not necessarily linear).
RD50	Dose producing a 50% response.
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation.
RoC/ROC	Report on carcinogens.
RR	Risk Ratio/Relative Risk is a measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. A value greater than 1.0 indicated a positive association between exposure and disease. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
rsen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
RSEN	A notation indicating the substance is a respiratory sensitiser. RSEN is used in place of SEN when specific evidence of sensitisation by the inhalation route is confirmed by human or animal data. An ACGIH® term.

TERM	MEANING
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
SK:DIR(IRR)-SEN	Skin notation indicating the potential for direct irritant effects and immune-mediated reactions following exposure of the skin. A NIOSH term.
SMR	Standardised Mortality Ratio is a measure of the strength or association between exposure and mortality; a form of Relative Risk (RR) in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard). By convention, the figure is usually multiplied by 100 [an SMR of 200 corresponds to a RR of 2.0]. A *value greater than 100/1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
STEL	The 15-minute time weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15-minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour work day and a 40-hour work week, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40-hour week. A WorkSafe term.
WES-Ceiling	A concentration that should not be exceeded at any time during any part of the working day.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

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