Workplace Exposure Standard (WES) review

2-ETHOXYETHYL ACETATE
(CAS NO: 111-15-9)

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Te Kāwanatanga o Aotearoa
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WORKSAFE
Mahi Haumaru Aotearoa

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for 2-ethoxyethyl acetate should be changed.

It considers the potential for exposures to 2-ethoxyethyl acetate 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 2-ethoxyethyl acetate, which is currently set at a **WES-TWA** of 5ppm (27**mg/m³**) with a ***skin*** notation, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 12th Ed., November 2020 (WorkSafe, 2020).

The WES recommended in this document is a guidance value, not a prescribed exposure standard. The intention is for it to be used as **risk criteria** for health risk assessment and risk management purposes and to be applied or interpreted only by people with appropriate training and experience. The value proposed in this document is considered by WorkSafe to be a health-based WES. This means it is based on minimising health risk and does not take the practicability of achieving or measuring the value into consideration. This also means that in some instances the current analytical or sampling methods will not be sensitive enough to allow measurement at a level sufficiently below the WES to assess risk with a high degree of confidence. In this case there will be some uncertainty as to whether risk is suitably managed. As with any risk assessment, the uncertainties inherent in the assessment need to be considered and minimised so far as is reasonably practicable through good risk assessment and control.

We consider it critical to set a health-based value as risk criteria, so that risk assessment is based on an actual understanding of health risk, rather than merely measuring a level of exposure.

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: Ethylene glycol monoethyl ether acetate; Ethyl glycol acetate; 2-EEA; EGEEA.

2.0 Chemical and physical properties

2-Ethoxyethyl acetate is a colourless liquid with a mild, ethereal odour at room temperature (**ECHA RAR**, 2008; **ACGIH®**, 2001).

An odour threshold of 5ppm has been reported for 2-ethoxyethyl acetate (ACGIH®, 2001).

Chemical and physical properties of 2-ethoxyethyl acetate include:

Formula	$C_6H_{12}O_3$
Molecular weight	132.16 g/mol
Physical form	Colourless liquid
Specific gravity	0.975 g/mL at 20°C
Melting point	-61.7°C
Boiling point	156.4°C
Vapour pressure	270 Pa at 20°C
Saturated vapour pressure	1.2 torr at 20°C
Flash point	Closed cup: 49°C
Ignition temperature	380°C
Solubility	Water: soluble, 23 g/100g at 20°C; completely miscible with aromatic hydrocarbons
Partition coefficients	$\log K_{OW}$ = 0.24 $\log K_{OC}$ = 0.32
Conversion factors	1 ppm = 5.44 mg/m³ at 25°C, 760 torr 1 mg/m³ = 0.185 ppm at 25°C, 760 torr

ECCC, 2009; ECHA RAR, 2008; ACGIH®, 2001

TABLE 1: Physicochemical properties of 2-ethoxyethyl acetate

Health-related hazard classifications for 2-ethoxyethyl acetate:

SUBSTANCE	CAS NUMBER	CLASSIFICATION
Ethanol, 2-ethoxy-, acetate	111-15-9	6.1D (All); 6.1D (O); 6.1E (D); 6.3B; 6.4A; 6.8A; 6.9B (All); 6.9B (I)

TABLE 2:
HSNO health-related hazard classifications of ethanol, 2-ethoxy-, acetate (**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

2-Ethoxyethyl acetate is used primarily as a chemical intermediate with smaller quantities used as a solvent (**AICIS**, 2014; ECHA RAR, 2008).

Industrial solvent uses include: lacquers, varnishes and paints; printing inks; cleaning agents; photographic processes; in manufacturing coatings and adhesives; and, in the semi-conductor industry. Wide-dispersive and non-industrial uses are reported to be historic (AICIS, 2014; ECHA RAR, 2008).

Occupational exposure to 2-ethoxyethyl acetate can occur during production, storage, transportation and end-use.

Workers can be exposed to 2-ethoxyethyl acetate via inhalation, and eye and skin contact (ECHA RAR, 2008).

The number of workers exposed or potentially exposed to 2-ethoxyethyl acetate in New Zealand workplaces is unknown.

4.0
Health effects

IN THIS SECTION:

2-Ethoxyethyl acetate has a common metabolite with 2-ethoxyethanol, 2-ethoxyacetic acid, which is considered to be the ultimate toxicant for both substances (**SCOEL**, 2007).

As 2-ethoxyethyl acetate is metabolised through 2-ethoxyethanol, toxicological studies with either substance are relevant to the toxicological profiles of both substances (**DFG**, 2008).

4.1 Non-cancer

Humans

The **IPCS** review of 2-ethoxyethanol summarised the acute toxicity in exposed humans:

> "Acute toxicity (including severe symptoms and death) has been observed after consumption of between 40 and 200 ml 2-ethoxyethanol (equivalent to approximately 600 and 3,000 **mg/kg** body weight) (Fucik, 1969; Bonitenko *et al*., 1990). Two phases of poisoning have been described. A temporary mild state of stupor and nausea ensued in some cases immediately after the 2-ethoxyethanol consumption. Patients then remained symptomless for 3–18 h, followed by gastrointestinal disturbances, nausea, vomiting, pain in the epigastral region, diarrhoea and central nervous system disturbances (weakness, headache, ataxia, psychomotoric excitation and coma)." (References cited in IPCS, 2010).

The New Zealand EPA classifies ethanol, 2-ethoxy-, acetate as a 6.1D and 6.1E substance – a substance that is acutely toxic (EPA, 2020).

The **NIOSH** Skin Notation Profile for ethoxyethyl acetate summarised the irritation/corrosion potential:

> "The overall data indicate that at most, **2-EEA** is a mild irritant. The effects are rapidly reversible and the appearance of irritation is dependent on the duration of exposure. This assessment is for occupational scenarios with daily exposures (typically 8 to 12 hours) intermediate between a duration that causes mild irritation (24 hours) and a duration that does not cause irritation (4 hours). Based on the minimal irritation observed even at 24 hours with constant contact, the weight of evidence from standard skin irritation tests suggests that 2-EEA is not likely to be a significant skin irritant in typical workplace scenarios." (NIOSH, 2014).

The NIOSH Skin Notation Profile for ethoxyethyl acetate summarised the sensitisation potential:

> "No occupational exposure studies or diagnostic (human patch) studies were identified that investigated the skin sensitization potential of 2-EEA in humans. Zissu [1995] conducted a Magnusson Kligman [guinea pig maximization test (**GPMT**)] on 30 guinea pigs (10 guinea pigs were controls and 20 guinea pigs were treated). Using a 10% concentration as the challenge, the authors found no evidence of skin sensitization. Based on the results of the single GPMT available that indicate that 2-EEA is not a potential skin sensitizer, 2-EEA is not assigned the **SK: SEN** notation." (NIOSH, 2014).

The IPCS review of 2-ethoxyethanol summarised the repeat dermal and inhalation dose toxicity in exposed humans:

> "In a well-conducted cross-sectional study (Kim *et al*., 1999), effects on white blood cells, suggestive of bone marrow depression, were observed in a group of 57 painters exposed to 2-ethoxyethyl acetate (along with several other substances, including toluene, ethylbenzene, xylene, butanol, isopropanol, ethanol, ethyl acetate, butyl acetate, methyl isobutyl ketone and nonane). White blood cell and granulocyte counts were reduced in both exposure groups (categorized as high [n = 27] and low [n = 30]), in an exposure-related manner. Those painters exposed to mean concentrations of 17 mg 2-ethoxyethyl acetate/m^3 [3.1 ppm] (approximately equivalent to 11 mg 2-ethoxyethanol/m^3 [3.0 ppm]) (range from not detected to 68 mg 2-ethoxyethanol/m^3 [18 ppm]) had a statistically significantly lower white blood cell and granulocyte count (P < 0.05), although this was not considered by the authors to be clinically significant. A statistically significantly higher proportion of all exposed painters had leukopenia (6/57 or 11%, five of which were in the high exposure group) compared with controls (0/41) (P < 0.05), and bone marrow hypoplasia was noted in the three leukopenic men examined. The effects remained after controlling for several potentially confounding factors (smoking and alcohol consumption, age and duration of work).
>
> "The incidence of anaemia and granulocytopenia was significantly (P = 0.04) increased in a group of 94 United States shipyard painters (mean age 38 ± 12 years) exposed to low levels (8-h TWA 0–80.5 mg/m^3 [0-22 ppm], mean 9.9 mg/m^3 [2.7 ppm]) of 2-ethoxyethanol (along with several other substances, including 2-methoxyethanol) for a mean of 8 (± 7) years, as compared with 55 controls (mean age 48 ± 10 years; duration of employment 22 ± 11 years) (Welch & Cullen, 1988). Haemoglobin levels in these workers had declined since first employment, but were not related to duration of exposure. Exposed workers also had a slightly higher prevalence of low polymorphonuclear leukocyte counts. Bone marrow hypoplasia was also observed in a survey of seven printers exposed to 2-ethoxyethanol and other substances (Cullen *et al*., 1983).
>
> "Low haemoglobin and haematocrit values were observed in women exposed to 2-ethoxyethyl acetate at a level corresponding to 35 mg 2-ethoxyethanol/m^3 [9.5 ppm] (geometric mean) in silk screening; they were also exposed to small amounts of toluene and methyl isobutyl ketone. Haemoglobin, haematocrit and red blood cell count showed a statistically significant negative association with exposure to 2-ethoxyethyl acetate. There was no effect on the leukocyte, granulocyte or platelet counts, and no effect on erythropoiesis was observed in men exposed to a geometric mean concentration of 18 mg/m^3 [4.9 ppm] (Loh *et al*., 2003)." (References cited in IPCS, 2010).

The New Zealand EPA classifies ethanol, 2-ethoxy-, acetate as a 6.3B and 6.4A substance – a substance that is mildly irritating to the skin, and irritating to the eye, respectively (EPA, 2020).

The IPCS review of 2-ethoxyethanol summarised the reproductive/developmental toxicity in exposed humans:

> "In the three relevant epidemiological investigations identified, reduced sperm production was consistently observed in populations occupationally exposed to mean 2-ethoxyethanol concentrations of 9.9 [2.7 ppm] or 24 mg/m³ [6.5 ppm] (with maximum levels up to 88 mg/m³ [24 ppm]), along with other substances (Welch *et al*., 1988; Ratcliffe *et al*., 1989; Schrader *et al*., 1996). Welch *et al*. (1988) examined the semen of 73 painters (mean age 37.5 years, range 19–62 years), employed for an average of 7.9 years (range 0.5–33 years) in a United States shipyard and exposed to a TWA concentration of 0–80.5 mg/m³ [0–22 ppm], with a mean of 9.9 mg/m³ [2.7 ppm] (matched with 40 controls: mean age 47.9 years [range 28–64 years], employed for 22 years [range 7–42 years]). Painters had an increased prevalence of oligospermia and azospermia (odds ratio [**OR**] = 1.85; 95% confidence interval [**CI**] = 0.6–5.6).
>
> "The cross-sectional study of Ratcliffe *et al*. (1989) involved 37 men exposed to 2-ethoxyethanol used as a binder slurry in a United States metal castings process and 39 non-exposed controls. Full-shift breathing-zone exposures ranged from non-detectable to 90 mg/m³ [24 ppm] (geometric mean concentration of 25 mg/m³ [6.8 ppm]). Urine measurements of the metabolite **EAA** ranged from nondetectable to 163 **mg/g** creatinine. A marginal, but statistically significant (P = 0.05), reduction in the average sperm count per ejaculate was found among the exposed workers compared with controls, after adjustment for age, smoking, alcohol and caffeine consumption, urogenital disorders, fever and other illnesses.
>
> "In a case–control study of 1019 men in Belgium with a clinical diagnosis of infertility or reduced fertility, there was a significant association between this diagnosis and the detection of EAA in the urine (OR = 3.11, P = 0.004) (Veulemans *et al*., 1993). Strong associations were reported between detection of EAA and exposure to paint products (P < 0.0001), glues (P = 0.004), solvents (P = 0.017), degreasers and cleaning products (P = 0.02) and petroleum products and fuels (P = 0.027).
>
> "There was no consistent evidence of effects on male or female reproductive ability in other investigations of men or women exposed to 2-ethoxyethanol, although most of these studies are limited by the lack of analyses for associations with 2-ethoxyethanol specifically (Beaumont *et al*., 1995; Schenker *et al*., 1995; Swan *et al*., 1995; Correa *et al*., 1996; Gray *et al*., 1996; Ha *et al*., 1996; Schenker, 1996; Swan & Forest, 1996; Chia *et al*., 1997)." (References cited in IPCS, 2010).

The New Zealand EPA classifies ethanol, 2-ethoxy-, acetate as a 6.8A substance – a substance that is a known or presumed human reproductive or developmental toxicant (EPA, 2020).

The DFG review of ethylene glycol monethyl ether summarised the genotoxic potential in exposed humans:

> "Two groups of 19 workers exposed to **EGEE** (2.9 **ml/m³**), EGEE acetate (0.5 ml/m³) and ethylene glycol monobutyl ether (0.5 ml/m³) had urinary ethoxyacetic acid and butoxyacetic acid concentrations of 53.2 and 0.2 **mg/l** urine on Monday before the shift and respectively, of 53.8 and 16.4 mg/l urine on Tuesday after the shift. The numbers of **SCE**s and micronuclei were not increased in lymphocytes that had been obtained from blood samples collected on Tuesday after the shift (Söhnlein *et al*. 1993)." (Reference cited in DFG, 2008).

The New Zealand EPA classifies ethanol, 2-ethoxy-, acetate as a 6.9B substance – a substance that is harmful to human target organs or systems (EPA, 2020).

Animals

The IPCS review of 2-ethoxyethanol summarised the acute toxicity in experimental animals:

> "2-Ethoxyethanol is of low to moderate acute toxicity in laboratory animals following oral exposure, with reported median lethal doses (**LD_{50}**s) in rats ranging from 2,125 to 5,490 mg/kg body weight (Laug *et al*., 1939; Smyth *et al*., 1941; Carpenter, 1947; Carpenter *et al*., 1956; Stenger *et al*., 1971; Truhaut *et al*., 1979; Krasavage & Terhaar, 1981; Dow Chemical Company, unpublished data, cited in Clayton & Clayton, 1982; Cheever *et al*., 1984). It is of low toxicity following inhalation or dermal exposure, with median lethal concentrations (**LC_{50}**s) of 16,000 mg/m³ (4 h) in rats and 5,500–7,400 mg/m³ (7 or 8 h) in rats and mice (Werner *et al*., 1943a; Pozzani *et al*., 1959; Shell, unpublished data, cited in Tyl *et al*., 1988; ECETOC, 1995) and dermal LD50s of 3,314–3,920 mg/kg body weight (covered application for 24 h) in rabbits (Carpenter *et al*., 1956; Krasavage & Terhaar, 1981; Daughtrey *et al*., 1984). Target sites of 2-ethoxyethanol-induced acute toxicity include the haematopoietic system, liver, kidneys and stomach." (References cited in IPCS, 2010).

The IPCS review of 2-ethoxyethanol summarised the irritation/corrosion potential in experimental animals:

> "2-Ethoxyethanol and its acetate have only low potential for irritation of skin and eyes (Werner *et al*., 1943b; Carpenter & Smyth, 1946; Truhaut *et al*., 1979; Krasavage & Terhaar, 1981; Barbee *et al*., 1984; Daughtrey *et al*., 1984; Kennah *et al*., 1989)." (References cited in IPCS, 2010).

The IPCS review of 2-ethoxyethanol summarised the sensitisation potential in experimental animals:

> "2-Ethoxyethanol has not been shown to be a skin sensitizer in the guinea-pig by the maximized Magnusson and Kligman method (Zissu, 1995)." (Reference cited in IPCS, 2010).

The ECHA RAR of 2-ethoxyethanol summarised the repeat inhalation dose toxicity in experimental animals:

> "In experimental animals, the most prominent adverse effects related to repeated exposures to 2-ethoxyethanol were evident in the haematopoietic system in both genders and in the male reproductive organs. Besides, adverse effects in a number of other organs (kidneys: tubular degeneration, adrenal gland hypertrophy, thymus atrophy, liver cell degeneration) were seen, but there were considered of lower significance since the dosages where they occurred were relatively high, their occurrence was less consistent across studies or changes were not severely graded."
>
> "Mild haemolytic anaemia and corresponding indirect effects such as increased hemosiderin deposition in the spleen and intensified extramedullary haematopoiesis were observed in a number of studies that included at least a basic set of haematology parameters. The lowest effective dose was 186 **mg/kg bw/day** for the oral route (Stenger *et al*., 1971, 13-week study, rat and dog) and 400 ppm (1,480 mg/m^3 [403 ppm]) for the inhalation route (13-week study, rat) (Barbee *et al*.,1984, Bio/dynamics Inc., 1983). Marked anaemia was observed at dosages of 10,000ppm in drinking water (about 800 mg/kg bw/day) (**NTP**, 1993).
>
> "Other effects included transient leucopoenia during the first weeks of treatment (NTP, 1993), and a reduction of myeloid cells in the spleen (Werner, 1943) that along with thymus atrophy (NTP, 1993, Ma-Hock *et al*., 2005) might indicate an immunosuppressive potential. However, its evidence is weak due to lack of consistency among studies. Leucocytosis and the shift to immature granulocytes could be caused by degenerative-inflammatory lesions in organs (most likely the testes effects in the 13-week study, NTP, 1993).
>
> "Adverse effects on the blood and haematopoietic system occurred at the same 2-ethoxyethanol concentrations than adverse effects on the male reproductive system."
>
> "The effects of 2-ethoxyethanol on the male reproductive system have been intensively investigated. Degenerative changes in the germinal epithelium of the seminiferous tubules were consistently noted in the rat, mouse, rabbit and dog following exposure to 2-ethoxyethanol through the inhalation, oral route or by subcutaneous injection. These effects include testicular atrophy, degeneration of testicular tubules, germ maturation arrest and depletion of mature stages of germ cells, decrease in sperm counts and motility, and an increase in the number of abnormal sperm cells.
>
> "The lowest effective dose (**LOAEL**) where testes toxicity occurred was 186 mg/kg bw/day estimated in a 13-week rat study (Stenger *et al*., 1971). Much higher dosages were needed when 2-ethoxyethanol was administered by feed. Via inhalation, the lowest effective concentration was 400 ppm (1,480 mg/m^3) in rabbits (Barbee *et al*., 1984, Bio/Dynamics Inc., 1983)." (References cited in ECHA RAR, 2008).

The ECHA RAR of 2-ethoxyethanol summarised the reproductive/developmental toxicity in experimental animals:

> "Experimental data from studies with mice demonstrated that 2-ethoxyethanol adversely affects male reproductive organs (testes atrophy) as well as sperm parameters and sperm morphology. 2-ethoxyethanol was further shown to adversely affect reproductive capability and capacity in both sexes for at least one generation.

"A **NOAEL** (fertility) of approximately 800 mg/kg bw/day was derived from a fertility study in mice after continuous exposure via drinking water (Lamb *et al*. 1985).

"It is however evident from various other studies (c.f. Table 4.1.2.9) using different species and applying different routes of exposure, that 2-ethoxyethanol specifically affects male reproductive organs (testes atrophy) and is spermatotoxic at clearly lower dose/concentration ranges depending on which parameters had been determined.

"A **NOAEC** (male reproductive organ toxicity/ spermatotoxicity) of 100 ppm was derived from a 13 week repeated dose toxicity study in rabbits (Bio/ dynamics Inc 1983; Barbee *et al*. 1984) and a NOAEL (male reproductive organ toxicity/ spermatotoxicity) of 93 mg/kg bw/day was derived from a 13 week repeated dose gavage study in rats (Stenger *et al*. 1971). A NOAEL (male reproductive effects) of 1,250 ppm in drinking water (109mg/kg bw/d) was established from a 13 week repeated dose study in rats (NTP 1993).

"In addition studies on rabbits, rats and mice with the inhalatory, oral and dermal route of exposure consistently demonstrated that 2-ethoxyethanol adversely affects embryonic and fetal development in terms of embryo-/ fetomortality, fetal growth retardation and visceral/skeletal malformations and variations in a dose-related manner. Significantly increased incidences of these developmental effects were induced already at dose levels without obvious maternally toxic effects, respectively borderline effects. Comparable effects could be also revealed by use of the dermal route of exposure. The teratogenic effects such as increase in skeletal and cardiovascular malformations were seen predominantly in rats and rabbits, whereas exencephaly and cleft palate were only seen in the mouse.

"A NOAEC (developmental toxicity) of 10 ppm was derived from the rat study with inhalation exposure (Doe 1984b; Tinston *et al*. 1983a). A NOAEL/ developmental toxicity of 23 mg/kg bw/day was derived for the oral route from studies with rats (Stenger *et al*., 1971). A LOAEL/developmental toxicity of 930-1,255 mg/kg bw/day was derived for the dermal route from the study of Hardin *et al*., 1984." (References cited in ECHA RAR, 2008b).

The NIOSH Skin Notation Profile for ethoxyethyl acetate noted:

"Specialty studies were identified that evaluated biological system/ function specific effects, such as reproduction and developmental effects following dermal exposure to 2-EEA. Hardin *et al*. [1984] applied 0.35 mL of pure, undiluted 2-EEA to adult rats 4 times per day, for a total daily dose of 1.4 mL [corresponding to 1,365 mg/day], on days 7 to 16 of gestation. Based on the average body weight provided on gestation days 5, 7, 12, 17, and 21, an average daily body weight of approximately 234 grams was estimated, giving a dose of 5,830 mg/kg-day of 2-EEA. Compared to water controls, treatment with 2-EEA caused maternal toxicity that manifested as significant reductions in maternal body weight gain, gravid uterus weights, and extragestational body weight gains. 2-EEA was also embryotoxic, as reflected in significantly higher frequencies of completely resolved litters, significantly increased number of dead implants per litter, significantly reduced number of live fetuses per litter, significantly reduced body weight of live fetuses, and significantly increased total cardiovascular malformations and skeletal variations (total ribs, vertebrae, and reduced ossification variations) [Hardin *et al*. 1984]. A Lowest Observed Adverse Effect Level (LOAEL) of 5,830 mg/kg-day, the only dose tested, for maternal and developmental toxicity can be established from this study. 2-EEA is expected

to be readily hydrolyzed *in vivo* to 2-ethoxyethanol and acetate [Hardin *et al*. 1984; ACGIH 2001b]. In the Hardin *et al*. [1984] study, at equimolar doses of 2-EEA and 2-ethoxyethanol, 2-EEA caused even more severe maternal, embryo, and fetal toxicity than did 2-ethoxyethanol. In an earlier study, Hardin *et al*. [1982] observed significant increase in resorptions, decreases in number of live fetuses per litter, decreases in fetal body weight, and an increase in the incidence of visceral malformations (predominantly of the cardiovascular system) and skeletal variations in rats dermally exposed 4 times/day to 0.25mL/application of 2-ethoxyethanol [corresponding to 1 mL/day] and intrauterine death in rats dermally exposed 4 times/day to 0.50mL/application of 2-ethoxyethanol [corresponding to 2mL/ day] during gestation days 7 to 16, followed by a 5-day post exposure period. A LOAEL of 3,445mg/kg-day, derived from the group that received 1mL/ day, for developmental effects can be established in the absence of maternal toxicity from these studies [Hardin *et al*. 1982, 1984]. 2-EEA is considered a potential reproductive and developmental toxicant following repeated dermal exposure.

"Use of the developmental toxicity studies by Hardin *et al*. [1982, 1984] to determine whether dermal application of 2-EEA is a systemic toxicant is hindered by dosing regimen, since a LOAEL was identified at the only dose tested." (References cited in NIOSH, 2014).

The NIOSH Skin Notation Profile for ethoxyethyl acetate concluded:

"... *in vitro* evaluations of the skin permeability of 2-EEA [Dugard *et al*. 1984; Barber *et al*. 1992] indicate that it is readily absorbed by the skin. Toxicity studies indicate 2-EEA is not acutely toxic following dermal exposure; however, developmental toxicity studies that utilized high dermal doses of 2-EEA showed the potential of the substance to cause maternal and developmental toxicity [Hardin *et al*. 1984]. Therefore, on the basis of the data for this assessment, 2-EEA is assigned the **SK: SYS** notation." (References cited in NIOSH, 2014).

The IPCS review of 2-ethoxyethanol summarised genotoxic potential in experimental animals and *in vitro* test systems:

"The available information on the genotoxicity of 2-ethoxyethanol suggests that 2-ethoxyethanol may have some potential to induce cytogenetic damage *in vitro*, although this was not reflected in *in vivo* studies in mice. There is no evidence that it induces mutations.

"In the limited *in vivo* database, there was no evidence of the induction of micronuclei in the bone marrow of Swiss Webster or CD-1 mice given single intraperitoneal injections of 2-ethoxyethanol (up to 2,000 or 3,000mg/kg body weight) (Guzzie *et al*., 1986; Elias *et al*., 1996), 2-ethoxyethyl acetate (no details of dose levels given in the published abstract) (Slesinski *et al*., 1988) or EAA (up to 200mg/kg body weight) (Elias *et al*., 1996).

"Neither 2-ethoxyethanol nor its acetate was mutagenic in several *in vitro* assays in *Salmonella typhimurium* (eight different strains tested, in both the presence and absence of metabolic activation) (Ong, 1980; Shimizu *et al*., 1985; Zeiger *et al*., 1985; Guzzie *et al*., 1986; Slesinski *et al*., 1988; Hüls AG, 1989; Hoflack *et al*., 1995) or in a limited number of studies in cultured mammalian cells (Guzzie *et al*., 1986; Myhr *et al*., 1986; Slesinski *et al*., 1988). Mixed or equivocal results have been reported for the induction of

chromosomal aberrations, micronuclei or sister chromatid exchange by 2-ethoxyethanol or 2-ethoxyethyl acetate in various mammalian cell lines: in Chinese hamster ovary cells, positive (for 2-ethoxyethanol) (Guzzie *et al*., 1986; Galloway *et al*., 1987) and equivocal (for 2-ethoxyethyl acetate) (Slesinski *et al*., 1988) results were reported for induction of chromosomal aberrations in the absence of metabolic activation, whereas in the presence of activation, 2-ethoxyethanol was positive (Slesinski *et al*., 1988) and 2-ethoxyethyl acetate was negative (Guzzie *et al*., 1986; Galloway *et al*., 1987). 2-Ethoxyethanol failed to induce chromosomal aberrations in Chinese hamster lung (V79) cells (Elias *et al*., 1996) and human lymphocytes (Villalobos-Pietrini *et al*., 1989; Elias *et al*., 1996) without activation. An equivocal response was reported for the induction of micronuclei in Chinese hamster V79 cells (Elias *et al*., 1996). 2-Ethoxyethanol induced sister chromatid exchange in Chinese hamster ovary cells in both the presence and absence of activation (Guzzie *et al*., 1986; Galloway *et al*., 1987), whereas the acetate was negative (Slesinski *et al*., 1988). Sister chromatid exchange was also induced in human lymphocytes treated with 2-ethoxyethanol in the absence of metabolic activation (Villalobos-Pietrini *et al*., 1989); in Chinese hamster V79 cells, an equivocal result was reported (Elias *et al*., 1996). 2-Ethoxyethanol did not induce morphological transformation or aneuploidy *in vitro*, although it did show weak potential to interfere with mitotic division (Elias *et al*., 1996). Although neither of the two principal metabolites of 2-ethoxyethanol, **EALD** and EAA, was mutagenic in *S. typhimurium* (Hoflack *et al*., 1995), the aldehyde consistently tested positive for numerous cytogenetic end-points *in vitro*, although results for the acid metabolite were negative or equivocal (Elias *et al*., 1996)." (References cited in IPCS, 2010).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] has no evaluation on the carcinogenic potential of 2-ethoxyethyl acetate (IARC, 2019).

The US National Toxicology Program [**NTP**] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of 2-ethoxyethanol (NTP RoC, 2016).

The New Zealand EPA has not classified 2-ethoxyethyl acetate as a 6.7A or 6.7B substance – substances that are respectively known or presumed, or suspected human carcinogens (EPA, 2019).

Humans

The ECHA RAR of 2-ethoxyethanol noted that there was no data on exposure and carcinogenicity in humans (ECHA RAR, 2008b).

Animals

The SCOEL review of 2-ethoxyethanol and 2-ethoxyethyl acetate summarised the data on exposure and carcinogenicity in experimental animals:

"No valid data on the carcinogenicity of 2-ethoxyethanol are available.

"Groups of 50 rats and 50 mice of both sexes were administered 2-ethoxyethanol by gavage in a 2-year study at dose levels of 0, 500, 1,000 or 20,000 mg/kg body weight. Testicular atrophy was observed in male rats that died early in this study and in the medium- and high-dose male mouse groups. Gross lesions noted at necropsy indicate that chronic treatment of

rats with 2-ethoxyethanol at dose levels of 500 or 1,000 mg/kg body weight caused an apparent enlargement of the adrenal gland in male rats and interfered with the development of spontaneous lesions of the spleen (males and females), pituitary (males and females), testis (males), and subcutaneous tissue in the mammary gland region (females) that commonly occur in the aging Fischer 344/N rat. Histopathological data of this study were not reported (Melnick 1984). NTP never finalized this 2-year study; conclusions for carcinogenicity can therefore not be derived." (References cited in SCOEL, 2007).

4.3 Absorption, distribution, metabolism and excretion

The SCOEL review of 2-ethoxyethanol and 2-ethoxyethyl acetate summarised the absorption, distribution, metabolism and excretion (**ADME**):

"Evidence from studies in experimental animals and in humans indicates that 2-ethoxyethanol is rapidly absorbed via the respiratory tract, the skin and the gastrointestinal tract. In humans under sedentary conditions, 64% of the inhaled 2-ethoxyethanol is taken up by the lung.

"In five volunteers dermally exposed to vaporised and liquid 2-ethoxyethanol, mean absorption rate of 2-ethoxyethanol vapour was 19±6 **cm/h** and of liquid 2-ethoxyethanol 0.7±0.3 **mg/cm²·h**. Vaporised and liquid 2-ethoxyethanol are therefore readily absorbed through the skin. In the combined inhalatory and dermal exposure when whole body surface is exposed to vapour, the uptake through the skin is estimated to be 42% of the total uptake 2-ethoxyethanol. Dermal uptake resulting from skin contact of both hands and forearms (about 2,000 cm^2) with liquid 2-ethoxyethanol for 60 minutes would exceed inhalatory uptake of the eight hour occupational exposure limit (about 5 ppm) by 20 times (Kezic *et al*. 1997).

"2-Ethoxyethyl acetate is metabolized to 2-ethoxyethanol. The main metabolic pathway for 2-ethoxyethanol is oxidation to 2-ethoxyacetic acid, which is further metabolised to its glycine conjugate N-ethoxyacetylglycine. Numerous *in vitro* and *in vivo* studies have shown the toxicity of 2-ethoxyethanol to be caused by the metabolite 2-ethoxyacetic acid (Henschler and Lehnert 1994) which is also the critical metabolite for 2-ethoxyethyl acetate. Ethanol inhibits the 2-ethoxyethanol degradation.

"2-Ethoxyethanol is excreted primarily in the urine, with a very small percentage of the dose exhaled via the lung as CO_2. In sedentary human subjects, 23-35% of the absorbed 2-ethoxyethanol was excreted in the urine as 2-ethoxyacetic acid. At all times after exposure, the amount of 2-ethoxyacetic acid eliminated was proportional to the 2-ethoxyethanol dose. 2-Ethoxyacetic acid is excreted in free form in the urine. According to results on individuals occupationally exposed to 2-ethoxyethanol, the half-life for the elimination of 2-ethoxyacetic acid lies between 50–60 hours; in volunteers with 4 hour exposure half-life was published with 21-24 hours. For rats half-lives of ca. 7 hours were determined (BUA 1995).

"Physiologically based pharmacokinetic (**PBPK**) models for 2-ethoxyethanol and 2-ethoxyethyl acetate in pregnant rats and humans have been developed. PBPK models of Gargas and coworkers (Gargas *et al*. 2000) were used with data from developmental toxicity studies with pregnant rats (Doe 1984) and from volunteer studies (non-pregnant) with 4 hour exposure to 2-ethoxyethanol or 2-ethoxyethyl acetate (Groeseneken *et al*. 1986, a, b, 1987 a, b; see below). The models considered 5 compartments, rapid hydrolysis

from 2-ethoxyethyl acetate to 2-ethoxyethanol, metabolism from 2-ethoxyethanol to 2-ethoxyacetic acid and its elimination in urine. Physiological parameters for an average pregnant woman were used to calculate human-equivalent **NAEL** (no adverse effect level) estimates, based on internal concentrations in rats exposed at previously determined NOELS for developmental toxicity (50ppm). For both substances the NAEL was estimated to be 25ppm. " (References cited in SCOEL, 2007).

The **ANSES** review of 2-ethoxyethanol and 2-ethoxyethyl acetate noted:

"EGEE is metabolised in humans as in animals by two main oxidative pathways:

- the action of alcohol and aldehyde dehydrogenase, which leads to the formation of EAA;
- the action of O-dealkylase leading to the formation of ethylene glycol (**EG**).

"Both these metabolic pathways can lead to the formation of CO_2 which is exhaled. The first pathway is likely responsible for the toxicity of **EGEE** and EGEEA due to the formation of EAA, the potentially toxic metabolite.

"The second pathway may be a detoxification pathway (Medinsky *et al*., 1990).

"It should be noted that ethanol has a higher affinity for alcohol dehydrogenase than EGEE. Thus, populations with relatively inactive alcohol-degrading enzymes metabolise alcohol more slowly and tend to eliminate EGEE and EGEEA much more slowly. This is the case for almost 50% of Asians, who have an inactive aldehyde dehydrogenase variant which is unable to metabolise acetaldehyde to acetate (Chen *et al*., 1999)." (Reference cited in ANSES, 2013).

The AICIS review of alkoxyethanols and their acetates noted:

"The alkoxyacetic acid metabolite has been shown to be excreted more slowly in humans than in rats (Government of Canada, 2002a; Government of Canada, 2002b; EU RAR, 2008; Government of Canada 2009a; Government of Canada 2009b)." (References cited in AICIS, 2014).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows 2-ethoxyethyl acetate exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2020).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia	5	27		
Austria	2	11	8	44
Belgium	2[1]	11[1]		
Canada – Ontario	5			
Canada – Québec	5	27		
Denmark	5	27	[10]	54
European Union[2]	2	11		
Finland	2	11		
France[3]	2	11		
Germany – **AGS**	2	10.8	16[4]	86.4[4]
Germany – DFG[5]	2	11	16[4]	88[4]
Hungary		27		108
Ireland	2	11		
Israel	5	27		
Italy[6]	2	11		
Japan – **MHLW**	5			
Japan – **JSOH**	5	27		
Latvia	2	11		
New Zealand[7]	5	27		
People's Republic of China		30		
Poland		11		
Romania	2	11		
Singapore	5	27		
South Korea	5	27		
Spain[6]	5	27		
Sweden	2	11		
Switzerland	2	11	16	88
The Netherlands		11		
Turkey	2	11		
USA – **NIOSH**	0.5	2.7		
USA – **OSHA**	100	540		
UK	10	55		

TABLE 3: Exposure standards for ethylene glycol monoethyl ether acetate from around the world

[1] Additional indication "D" means that the absorption of the agent through the skin, mucous membranes or eyes is an important part of the total exposure. It can be the result of both direct contact and its presence in the air.

[2] Indicative Occupational Exposure Limit Value (**IOELV**).

[3] Restrictive statutory limit values.

[4] 15 minutes average value.

[5] MAK value applies for the sum of the concentration of ethylene glycol monoethyl ether and its acetate in air.

[6] skin notation.

[7] Exposure can also be estimated by biological monitoring.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on 2-ethoxyethyl acetate were ANSES, SCOEL, DFG, ACGIH®, and Safe Work Australia.

5.2 ANSES

The Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail [French Agency for Food, Environmental and Occupational Health & Safety] review of 2-ethoxyethanol and 2-ethoxyethyl acetate concluded that an 8h-OEL of 1ppm (3.75mg/m³ at 20°C and 101**kPa** for 2-ethoxyethanol and 5.49mg/m³ for 2-ethoxyethyl acetate) and a 15-min **STEL** of 5ppm (18.75mg/m³ for 2-ethoxyethanol and 27.45mg/m³ for 2-ethoxyethyl acetate) could be recommended (ANSES, 2013).

Rationale:

> "The results of epidemiological and toxicological studies show that the critical effects observed following administration of EGEE and/or EGEEA are similar, as they are due to a common metabolite.
>
> The critical effects adopted are both haematotoxicity observed in humans and animals, and reproductive toxicity which has only been observed in animals. It should be noted that the doses at which these effects are observed are of the same order of magnitude, regardless of the administered compound, if ppm are used.
>
> "Therefore, the OELs were established from studies considering either EGEE or EGEEA.
>
> "The haematologic effects were demonstrated by several epidemiological studies, particularly that of Kim *et al*. (1999) which, because of its many limitations, could not be retained as the key study. The study by Barbee *et al*. (1984) was chosen as the key study because it is a subchronic exposure study conducted in male and female rabbits and rats, where the observed effects were also noted in workers. The NOAEL for haematological effects is 100ppm."

ANSES recommended 3 *safety factors* to extrapolate from the animal study derived NOAEL to an OEL:

> - SF_A = 3 ; Transposition from animals (rabbits) to humans
> - SF_H = 10 ; Variation in enzymatic metabolism according to ethnic origin: Caucasian/Asian polymorphism
> - SF_S = 3 ; Extrapolation from the subchronic exposure in the study (15 weeks) to whole life exposure.
>
> "This leads to the recommendation of an 8h-OEL of 1ppm, that is, 3.75mg/m³ at 20°C and at 101kPa for EGEE and 5.49mg/m³ for EGEEA.
>
> "The short-term deleterious effects of EGEE/EGEEA are not substantiated. Irritation was mentioned in some animal studies. However, given the reprotoxicity of these substances, special attention should be paid to women of childbearing age, to avoid exposure peaks during specific windows of exposure.
>
> "Under these conditions and in accordance with its previous work (AFSSET, 2008), the OEL Committee recommends a STEL equal to five times the 8h-OEL, that is, 5ppm (18.75mg/m³ for EGEE and 27.45mg/m³ for EGEEA).
>
> "The study by Kesic *et al*. (1997) conducted in volunteers clearly indicates significant dermal absorption of EGEE. Therefore, the skin notation should be attributed both to EGEE and EGEEA." (References cited in ANSES, 2013).

5.3 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] review of 2-ethoxyethanol and 2-ethoxyethyl acetate recommendation included:

> "2-Ethoxyethyl acetate and 2-ethoxyethanol show similar toxicity in animal experiments due to metabolism to the same critical metabolite (2-ethoxyacetic acid). As both substances may be used at the same time, it is necessary to limit exposure of the common critical metabolite. Evaluation of both substances together is therefore necessary.
>
> "The critical effects of 2-ethoxyethanol and 2-ethoxyethyl acetate are on reproduction and the blood, which are detected in experimental animals and in humans. As humans are more sensitive than animals, only human studies (even if they are of limited validity) are used for deriving an OEL.
>
> "For effects in humans on hematopoesis, effect levels of 2.6 ppm (maximum 21.5 ppm; Welch and Cullen 1988) and 3.0 ppm (maximum 18.3 ppm) and a level of no significant effects of 1.8 ppm (maximum 8.1 ppm) (Kim *et al*. 1999) were derived. Effects on sperm parameters were observed in workers exposed to about 17 ppm 2-ethoxyethanol with exposure being reduced during the study to 6.6 ppm (Ratcliffe *et al*. 1989). In the light of significant uncontrolled dermal uptake of 2-ethoxyethanol, which is expected to contribute to a high extent to internal exposure, as well as additional exposure to 2-methoxyethanol (which elicits the same effects), the concentrations of 2-ethoxyethanol reported in the air only account for inhalational uptake; if dermal uptake is avoided, concentrations in the air might be higher until effects occur.
>
> "If dermal absorption is avoided, an 8-h TWA of 2 ppm should protect from effects on hematopoesis and fertility. This TWA is consistent with the 8-h TWA of 1 ppm for 2-methoxyethanol, an analogous glycol ether with stronger hematotoxic and reproductive effects.
>
> "The TWA will prevent [sic] from developmental toxicity (NOAEL 50 ppm), provided that dermal exposure is avoided and the biological limit value is observed. This is in accordance with the proposal by Sweeney *et al*. (2001) who used a different approach based on developmental toxicity.
>
> "Sufficient data are not available to recommend a STEL (ACGIH 2001 a, b).
>
> "A skin notation is recommended as dermal absorption can contribute substantially to the total body burden." (References cited in SCOEL, 2007).

5.4 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] re-evaluations of ethylene glycol monoethyl ether (DFG, 2008b) and ethylene glycol monoethyl ether acetate (DFG, 2008a) concluded:

> "Since EGEE is readily absorbed through the skin and the toxic metabolite ethoxyacetic acid accumulates during the working week, systemic exposure to ethoxyacetic acid is decisive for toxicity and therefore the basis for deriving the MAK value. In 1992, the **BAT** value for EGEE was established at 50 mg ethoxyacetic acid/l urine (Henschler and Lehnert 1993 a). In 1994, the MAK value for EGEE was established on the basis of the findings obtained by Ratcliffe *et al*. (1989) since effects on sperm parameters could not be ruled out in the group of workers who excreted 85 ± 31.3 mg 2-ethoxyacetic acid/g creatinine (about 100 mg/l urine). A MAK value of 5 ml/m³ was established assuming that this concentration corresponded to ethoxyacetic acid

concentrations of 10 to 35 mg/l in the urine at the end of a working week. However, a new PBPK model shows that the concentration of EGEE of 5 ml/m³ after inhalation exposure alone corresponds to about 120 mg ethoxyacetic acid/l urine (95th percentile) at the end of a working week. Since effects on sperm may occur at about 100 mg ethoxyacetic acid/l urine and the BAT value is 50 mg ethoxyacetic acid/l urine, the MAK value has been lowered to 2 ml/m³; this correlates with the BAT value of 50 mg ethoxyacetic acid/l urine according to the PBPK model. In 2001, **Peak Limitation Category II** with an excursion factor of 8 was established for EGEE by analogy to other short-chain glycol ethers since the metabolite ethoxyacetic acid responsible for the critical systemic toxicity has a very long halflife and irritation is expected only above 50 ml/m³. This excursion factor has been retained.

"EGEE was not mutagenic *in vitro*, but showed clastogenicity at high concentrations. No genotoxicity was observed *in vivo* in a micronucleus test in mice. No classification in any of the germ cell mutagen categories is therefore required.

"In a carcinogenicity study, rats and mice were exposed for 2 years, and no tumours were observed by gross pathology. Since no comprehensive histopathological examinations were carried out, no conclusions can be drawn with regard to carcinogenicity. However, there is no evidence to justify a classification of EGEE in one of the Carcinogen Categories.

"A NOAEC of 50 ml/m³ was obtained for developmental toxicity in rats and rabbits. Visceral and skeletal defects and variations, and sometimes malformations as well, were observed in rats from 250 ml/m³. The incidence of skeletal defects and variations was increased in Dutch rabbits after 6-hour exposure to EGEE at 175 ml/m³ daily from days 6 to 18 of gestation; an increased incidence of malformations was observed at 160 ml/m³ after 7-hour exposure of white New Zealand rabbits from days 1 to 18 of gestation. Although the MAK value for EGEE has been lowered from 5 to 2 ml/m³, the margin between the NOAEC of 50 ml/m³, or between 160 ml/m³, that is, the concentration which led to an increased incidence of malformations in rabbits, and the MAK value is not high enough for a classification in **Pregnancy Risk Group C**. Therefore, EGEE remains in **Pregnancy risk group B**. The high absorption of EGEE and EGEE acetate through the skin and the accumulation of ethoxyacetic acid in humans has been taken into account here.

"Since EGEE is readily absorbed through the skin, the designation **H** has been retained and is justified.

"EGEE showed no sensitizing potential in a maximization test carried out in guinea pigs. No other studies or effects in humans are available. The substance is therefore not designated with **Sa** or **Sh**." (References cited in DFG, 2008b).

"In humans, ethylene glycol monoethyl ether acetate is deacetylated to ethylene glycol monoethyl ether with a half-life of 8 to 11 minutes (see documentation 2-Ethoxyethanol, 2-Ethoxyethyl acetate 1998, a translation of the 1994 German) and metabolized further to form the critical metabolite ethoxyacetic acid, which accumulates in the human body and is considered to be responsible for the haematotoxicity and reproductive toxicity. The profile of ethylene glycol monoethyl ether acetate is similar to that of ethylene glycol monoethyl ether; only the irritation potential to the skin and eyes is somewhat lower. It is therefore justified to assess the data of ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate together. For this reason, the data for ethylene glycol monoethyl ether acetate were documented together with those for ethylene glycol monoethyl ether in the supplement ethylene glycol monoethyl ether (documentation Ethylene glycol monoethyl ether 2008).

> "Since the MAK value for ethylene glycol monoethyl ether was lowered to 2 ml/m³ (see documentation Ethylene glycol monoethyl ether 2008), the MAK value for ethylene glycol monoethyl ether acetate has also been lowered from 5 to 2 ml/m³ by analogy.
>
> "Peak limitation category II with an excursion factor of 8, which was established by analogy to other short-chain glycol ethers, has been retained.
>
> "By analogy to ethylene glycol monoethyl ether (documentation Ethylene glycol monoethyl ether 2008), no classification in any of the germ cell mutagen or carcinogen categories is required.
>
> "The previous classification in pregnancy risk group B has also been retained (see documentation Ethylene glycol monoethyl ether 2008).
>
> "Since ethylene glycol monoethyl ether acetate is readily absorbed through the skin, the designation H has been retained and is justified (documentation Ethylene glycol monoethyl ether 2008). By analogy to ethylene glycol monoethyl ether, the substance is not designated with Sa or Sh (see documentation "Ethylene glycol monoethyl ether" 2008)." (DFG, 2008a).

5.5 ACGIH®

The ACGIH® review of 2-ethoxyethyl acetate concluded with recommendations that a **TLV-TWA** of 5 ppm [27 mg/m³] with a Skin notation for occupational exposure to 2-ethoxyethyl acetate, would minimise the potential for reproductive and developmental effects, primarily testicular atrophy reported in mice exposed by oral gavage to 2-ethoxyethyl acetate (ACGIH®, 2001).

Rationale:

> "Based upon the reported testicular effects (Nagano *et al*., 1979) and by analogy to the **TLV** for 2-ethoxyethanol (see *TLV Documentation* for 2-Ethoxyethanol), a TLV-TWA of 5 ppm, with a Skin notation, is recommended for 2-ethoxyethyl acetate. Sufficient data were not available to recommend **SEN** or carcinogenicity notations or a **TLV-STEL**." (ACGIH®, 2001).

5.6 Safe Work Australia

Safe Work Australia has recommended an 8-h TWA of 2 ppm (10.9 mg/m³) for 2-ethoxyethyl acetate to protect for reproductive and developmental effects in exposed workers. They further recommend a Sk (skin) notation based on evidence suggesting potential dermal absorption and adverse systemic effects in animals.

In their review they say "Limited data are available in humans. Critical effects include embryo mortality and growth retardation." (Safe Work Australia, 2019)

6.0 Analytical methods for the assessment of airborne 2-ethoxyethyl acetate

A common method to measure 2-ethoxyethyl acetate exposure is using NIOSH Method 1450, Issue 3 (NIOSH, 2003).

Using this method an air sample of up to 10 litres is collected onto a coconut shell charcoal solid sorbent tube using a flow rate of 0.01 to 0.2 litres per minute. Following desorption of the analyte using carbon disulphide, the sample is analysed using gas chromatography with flame ionisation detection (FID). This method can achieve a limit of detection of 1µg per sample, leading to reliable quantitation at airborne concentrations below 1ppm.

This method can be used to quantify samples at airborne concentrations below the proposed 8-hour WES-TWA value.

7.0
Discussion

WorkSafe's WES for 2-ethoxyethyl acetate has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates that 2-ethoxyethyl acetate is systemically toxic to humans, causing haematological and (male) reproductive effects. 2-Ethoxyethyl acetate is systemically toxic to experimental animals, causing haematological, reproductive and developmental effects.

Based on the aforementioned documentation, informed by the conclusions of the ANSES, SCOEL, DFG and ACGIH®, reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 5 ppm (27 mg/m^3) for 2-ethoxyethyl acetate, to be inadequate to manage health risks from possible workplace exposure:

- 2-Ethoxyethyl acetate is a potential haematological and reproductive toxicant in exposed workers (SCOEL, 2007; DFG, 2008b). The putative ultimate toxicant, 2-ethoxyacetic acid, is a common metabolite to both 2-ethoxyethyl acetate and 2-ethoxyethanol (SCOEL, 2007).
- 2-Ethoxyethyl acetate has shown no evidence of genotoxic potential, based on limited reported test systems (IPCS, 2010).
- The ANSES review of 2-ethoxyethanol and 2-ethoxyethyl acetate recommended an 8-hour OEL of 1 ppm (3.75 mg/m^3 for 2-ethoxyethanol and 5.49 mg/m^3 for 2-ethoxyethyl acetate) and a 15-min STEL of 5 ppm (18.75 mg/m^3 for 2-ethoxyethanol and 27.45 mg/m^3 for 2-ethoxyethyl acetate) to be protective against haematological and reproductive effects, based on the NOAEL from subchronic inhalation studies in rabbits and rats (Barbee *et al*., 1984 cited in ANSES, 2013).
- The SCOEL review of 2-ethoxyethanol and 2-ethoxyethyl acetate recommended an 8-hour TWA OEL of 2 ppm (8 mg 2-ethoxyethanol/m^3; 11 mg 2-ethoxyethyl acetate/m^3) to be protective against effects on haematopoiesis and fertility, if dermal absorption was avoided, based on studies in exposed humans (SCOEL, 2007).
- The DFG review of 2-ethoxyethyl acetate recommended a MAK value of 2 ppm (10.8 mg/m^3), defined as the sum of the concentrations of ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate in air, and confirmed a Pregnancy Risk Group B assignment. The MAK value was based on adverse sperm parameters in exposed workers who excreted about 100 mg 2-ethoxyacetic acid/L urine, that PBPK modelling indicated corresponds to air concentrations of 5 ppm, while 2 ppm corresponds to about 50 mg 2-ethoxyacetic acid/L urine (DFG, 2008a; DFG, 2008b).
- The ACGIH® review of 2-ethoxyethyl acetate concluded with recommendations that a TLV-TWA of 5 ppm [27 mg/m^3] would minimise the potential for reproductive effects reported in experimental animals (ACGIH®, 2001).

- The draft Safe Work Australia review of their WES for 2-ethoxyethyl acetate recommended a TWA of 2 ppm (10.9 mg/m^3), with a skin notation, to protect for reproductive and developmental effects in exposed workers, while citing the DFG's PBPK approach (Safe Work, 2019).
- The proposed WES-TWA of 2 ppm for the sum of 2-ethoxyethanol and 2-ethoxyethyl acetate is intended to protect exposed workers from potential haematological, reproductive and developmental effects.
- A ***skin*** notation is justified for 2-ethoxyethyl acetate, due to the reported significance of dermal absorption from contact with vapour or liquid 2-ethoxyethyl acetate (DFG, 2008b; SCOEL, 2007). Biological monitoring of workers is recommended to assess total exposures to 2-ethoxyethanol and 2-ethoxyethyl acetate and potential health risks.
- Available information indicates that 2-ethoxyethyl acetate is not a sensitiser (NIOSH, 2014), and a ***sen*** notation is not warranted.

8.0
Recommendations

WorkSafe considers its current WES-TWA 5 ppm (27 mg/m^3) for 2-ethoxyethyl acetate 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 2-ethoxyethyl acetate of 2 ppm (11 mg/m^3)
2. maintain a skin notation for 2-ethoxyethyl acetate.

Noting that the proposed WES-TWA for 2-ethoxyethyl acetate may not eliminate all risk, due to the potential contribution of dermal exposures from vapour and liquid to total body burden, so workplace exposures should be minimised.

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: https://portal.acgih.org/s/store#
ADME	Absorption, Distribution, Metabolism and Excretion.
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.
AICIS	Australian Industrial Chemicals Introduction Scheme – the regulatory scheme that administers the Australian law regulating the importation and manufacture of industrial chemicals in Australia. AICIS replaced the National Industrial Chemicals Notification and Assessment Scheme (**NICNAS**) on 1 July 2020.
ANSES	Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail [French Agency for Food, Environmental and Occupational Health & Safety].
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
BLV	Biological Limit Value.
CI	Confidence Interval.
cm/h	Centimetre per hour.
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.
EAA	2-Ethoxyacetic acid.
EALD	2-Ethoxyacetaldehyde.
ECCC	Environment and Climate Change Canada.
ECHA	The European Chemicals Agency (an agency of the European Union).
2-EEA	2-Ethoxyethyl acetate.
EG	Ethylene glycol.
EGEE	Ethylene glycol monoethyl ether.
EGEEA	Ethylene glycol monoethyl ethyl acetate.
EPA	The New Zealand Environmental Protection Authority.
GPMT	Guinea pig maximization test.
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the *skin notation* in the WorkSafe WES special guide.
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.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
IOELV	Indicative Occupational Exposure Limit Value (health-based, SCOEL parameter).
IPCS	International Programme on Chemical Safety – a World Health Organisation Programme.
JSOH	Japan Society for Occupational Health.
kPa	Kilopascal.

TERM	MEANING
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LOAEL	Lowest Observed Adverse Effect Level.
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 (e. g. 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. Values set by the DFG.
mg	Milligram or one thousandth of a gram.
$mg/cm^2 \cdot h$	Milligrams of substance per square cen¬timetre per hour [rate of skin absorption by area of skin exposed].
mg/g	Milligrams per gram.
mg/kg	Milligrams per kilogram.
mg/kg bw/ day or mg/ kg bw/d	Milligram of substance per kilogram body weight per day (exposure rate).
mg/m^3	Milligrams of substance per cubic metre of air.
mg/L or mg/l	Milligrams of a substance per litre.
MHLW	Japanese Ministry of Health, Labour and Welfare.
ml/m^3	Millilitres of substance per cubic metre of air; equivalent to ppm.
NAEL	No adverse effect level.
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
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.
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.
OEL	Occupational Exposure Limit (equivalent to a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
PBPK; PB-PK	Physiologically based pharmacokinetic: a modelling technique for predicting the absorption, distribution, metabolism and excretion [ADME] of substances in humans and other animal species.
Peak limitation category 2/II	Substances with systemic effects; Exclusion factor = 2 [default]; Duration 15 minutes, average value; Number per shift = 4; Interval = 1 hour. A DFG term.
ppm	Parts of vapour or gas per million parts of air.
Pregnancy Risk Group B	According to currently available information damage to the embryo or foetus cannot be excluded after exposure to concentrations at the level of the MAK and BAT values. A DFG term.

TERM	MEANING
Pregnancy Risk Group C	Damage to the embryo or foetus is unlikely when the MAK value or the BAT value is observed. A DFG term.
RAR	Risk Assessment Report.
Risk criteria	The terms of reference against which the significance of risk is evaluated. It is used to support decision making on health risk management. ISO 31000 2nd edition Risk Management – guidelines (2018).
RoC	Report on Carcinogens.
"Sa"	Sensitising to airways. A DFG MAK notation.
SCE	Sister Chromatid Exchange.
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.
sen	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.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
"Sh"	DFG MAK designation: *danger of sensitisation of the skin*.
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.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
SK: SEN	Skin notation indicating the potential for immune-mediated reactions following exposure of the skin. A NIOSH term.
SK: SYS	Skin notation indicating the potential for systemic toxicity following exposure of the skin. A NIOSH 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 workday and a 40-hour workweek, 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.
TWA	Time-weighted average exposure.
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-STEL / 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.
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

Appendix 3: References

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Notes

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