Workplace Exposure Standard (WES) review

TOLUENE
(CAS NO: 108-88-3)

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Te Kāwanatanga o Aotearoa
New Zealand Government

WORKSAFE
Mahi Haumaru Aotearoa

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1.0
Introduction

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

It considers the potential for exposures to toluene 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 toluene, which is currently set at a **WES-TWA** of 50 **ppm** (188 **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 are guidance values, not prescribed exposure standards. The intention is for them 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 values proposed in this document are considered by WorkSafe to be health-based WES. This means they are based on minimising health risk and do not take the practicability of achieving or measuring the values 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: Toluol; Methylbenzene; Benzene, methyl-; Phenylmethane; Monomethyl benzene.

2.0 Chemical and physical properties

Toluene is a clear, colourless liquid with a sweet, pungent odour like benzene at room temperature (AICIS, 2017; **ATSDR**, 2017; **ACGIH®**, 2007).

An odour threshold of 2.5 ppm (9.6 mg/m³) has been reported for toluene (ACGIH®, 2007).

Chemical and physical properties of toluene include:

Formula	C_7H8_8
Molecular weight	92.13 g/mol
Physical form	Colourless liquid
Specific gravity	0.8631 g/mL at 20°C
Melting point	-94.991°C
Boiling point	110.625°C
Relative vapour density	3.1 (air = 1)
Vapour pressure	6.8 torr at 0°C; 21.9 torr at 20°C; 59.3 torr at 40°C; 291.5 torr at 80°C
Saturation concentration	142,000 mg/m³ at 25°C
Flash point	Closed cup: 4°C; Open cup: 16°C
Autoignition temperature	480°C
Flammability limits	1.1–7.1%
Solubility	Water: 526 **mg/L** at 25°C; miscible with alcohol, chloroform, ether, acetone, glacial acetic acid, carbon disulphide
Partition coefficients	$\log K_{OW}$ = 2.73 $\log K_{OC}$ = 1.57–2.25
Conversion factors	1 ppm = 3.77 mg/m³ at 25°C, 760 torr 1 mg/m³ = 0.265 ppm at 25°C, 760 torr

ATSDR, 2017; ACGIH®, 2007

TABLE 1: Physicochemical properties of toluene

Health-related hazard classifications for toluene:

SUBSTANCE	CAS NUMBER	CLASSIFICATION
Benzene, methyl-	108-88-3	6.1D (All); 6.1D (O); 6.1D (I); 6.3A; 6.4A; 6.8B; 6.9B (All); 6.9B (I)

TABLE 2:
HSNO health-related hazard classifications of benzene, methyl- (**EPA**, 2020)

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

Toluene is used primarily as a chemical intermediate with smaller quantities used as a solvent, while non-isolated toluene from refinery streams is used in petrol to improve octane ratings as benzene-toluene-ethylbenzene-xylene (BTEX) mix (ATSDR, 2017; AICIS, 2017).

Chemical products from toluene include: benzene; xylene; and, toluene diisocyanate; while solvent uses include: in paints, coatings, gums, resins, rubber, and vinyl organosol (ATSDR, 2017; AICIS, 2017).

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

Workers can be exposed to toluene via inhalation, and eye and skin contact.

The number of workers exposed or potentially exposed to toluene in New Zealand workplaces is unknown, but would include both individuals working specifically with toluene and individuals exposed as a secondary effect of their workplace, for example, transport workers, and others working with or near combustion engines.

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The AICIS review of toluene summarised the acute toxicity in exposed humans:

> "Acute exposure of humans to the chemical at concentrations up to 375 mg/m^3 or less for single periods of 20 minutes to 3.5 hours did not result in adverse effects being observed (Government of Canada, 1992). Acute exposure to the chemical in the range of 750–5,625 mg/m^3 (200–1,500 ppm) caused dose-related central nervous system effects (**IPCS**, 1986). High acute exposures to the chemical (for example, 37,500 mg/m^3) during industrial accidents were characterised by initial central nervous system excitative effects (for example, exhilaration, euphoria, hallucinations), followed by a progressive impairment of consciousness, eventually resulting in seizures and coma (IPCS, 1986)." (References cited in AICIS, 2017).

The New Zealand EPA classifies benzene, methyl- as a 6.1D substance – a substance that is acutely toxic (EPA, 2020).

The AICIS review of toluene summarised the irritation/corrosion potential:

> "Single, short-term exposures to the chemical (750 mg/m^3 for eight hours) have reportedly caused transient eye and respiratory tract irritation with lachrymation at 1500 mg/m^3 (**WHO**, 1986). Nasal or ocular irritation in humans has been reported from airborne concentrations of the chemical of 100 ppm or above (**US EPA**, 2005)." (References cited in AICIS, 2017).

The New Zealand EPA classifies benzene, methyl- as a 6.3A and 6.4A substance – a substance that is irritating to the skin and to the eye (EPA, 2020).

The ACGIH® review of toluene noted that there was no data available on the sensitisation potential of toluene in humans (ACGIH®, 2007).

The ATSDR review of toluene summarised the repeat inhalation dose toxicity in exposed humans:

> "Dysfunction of the central nervous system is a critical human health concern following acute, intermediate, or chronic inhalation exposure to toluene. Chronic toluene abuse in humans has been associated with neurotoxic symptoms, narcosis, permanent damage to the central nervous system, and death. Self-reported neurological symptoms, reduced ability in tests of cognitive and neuromuscular function, and hearing and color vision loss have been observed in humans occupationally exposed to average concentrations ranging from 35 to 200 ppm; several occupational studies identify **NOAEL**s for these effects in the range of 20–187 ppm toluene. Performance deficits in tests of neurobehavior have also been observed in volunteers acutely exposed to controlled concentrations > 50 ppm." (References cited in ATSDR, 2017).

The ATSDR review of toluene noted the rationale for setting an **MRL** of 1 ppm (3.8 mg/m^3) for chronic-duration (365 days or more) inhalation exposure to toluene:

> "The chronic inhalation MRL is based on a NOAEL of 45ppm toluene for neurological effects based on a series of studies by the same group of investigators assessing subjective neurological symptoms, performance on psychomotor tasks, color vision, and hearing in groups of German photogravure

printers employed for an average duration of 13.5 years (Schäper *et al*. 2003, 2004, 2008; Seeber *et al*. 2004, 2005; Zupanic *et al*. 2002). These studies compared neurological end points in high-exposure printers (n = 106–181) and low-exposure tend-processors [sic] (n = 86–152). Current toluene air exposure levels for printers and end-processors were 24.6–26 and 3–3.5 ppm, respectively (measured twice yearly from 1996 to 2001). Historical exposure levels for printers prior to 1995 and prior to 1975 were 40 and 140 ppm, respectively. Historical exposure levels for end-processors prior to 1995 and prior to 1975 were 5 and 40 ppm, respectively. Using job history and current exposure and historical exposure levels, individual time-weighted average (**TWA**) exposure levels were calculated. The average TWA levels for printers and end-processors were calculated to be 45 and 10 ppm for subjects included in analyses by Schäper *et al*. (2003, 2008), 45 and 9 ppm for subjects included in analyses by Seeber *et al*. (2004, 2005) and Zupanic *et al*. (2002), and 43 and 9 ppm for subjects included in analyses by Schäper *et al*. (2004). Schäper *et al*. (2003, 2008) did not find any statistically significant differences in audiometric readings from four readings over 5 years in 181 printers, compared with 152 end-processors; Schäper *et al*. (2004) did not find any differences in color vision assessed 4 times over 5 years in 154 printers, compared with 124 end-processors; and Seeber *et al*. (2004, 2005) and Zupanic *et al*. (2002) did not find any increase in subjective neurological complaints or decreased performance in psychomotor tasks in 106–154 printers, compared with 86–124 end-processors. The NOAEL of 45 ppm was adjusted for continuous exposure (45 ppm x 5 days/7 days x 8 hours/24 hours = 10.7 ppm) and was divided by an uncertainty factor of 10 to account for human variability to derive the MRL of 1 ppm." (References cited in ATSDR, 2017).

The ATSDR review of toluene summarised the reproductive toxicity in exposed humans:

"Current data do not provide convincing evidence that acute or repeated inhalation exposure to toluene may cause reproductive effects in humans. Limited evidence in humans indicates that occupational exposure to toluene (and other solvents) may lead to an increased incidence of spontaneous abortion or decreased fecundity in female workers. One study reports increased risk of preterm birth with increasing environmental toluene exposure; however, concurrent exposure to multiple pollutants limits the conclusions that can be drawn from this study." (ATSDR, 2017).

The ATSDR review of toluene summarised the developmental toxicity in exposed humans:

"There are a number of published reports of birth defects, similar to those associated with fetal alcohol syndrome, that have been described in children born to women who intentionally inhaled large quantities of toluene or other organic solvents during pregnancy. Defects described include microcephaly, central nervous system dysfunction, growth deficiency, cranofacial and limb abnormalities, and reversible renal tubular acidosis. Studies of women exposed during pregnancy to much lower concentrations of toluene in the workplace are restricted to a retrospective study of 14 women in Finland occupationally exposed to mixed solvents that suggested that solvent exposure may increase risk for central nervous system anomalies and neural tube closure defects.

> "The reports of birth defects in solvent abusers suggest that high-level exposure to toluene during pregnancy can be toxic to the developing fetus. The available human data, however, do not establish causality between low-level or occupational exposure to toluene and birth defects, because of the small sample size and the mixed solvent exposure experienced by the subjects, the lack of other studies of possible birth defects in children of occupationally exposed women, and the likelihood that the high exposure levels experienced by pregnant solvent abusers (4,000–12,000 ppm) overwhelm maternal protection of the developing fetus from absorbed toluene. Experiments with pregnant mice demonstrated that 10-minute exposures to 2,000 ppm resulted in low uptake of toluene into fetal tissue and suggest that, at lower exposure levels, absorbed toluene is preferentially distributed to maternal adipose tissue before distribution to the developing fetus." (ATSDR, 2017).

The ATSDR review of toluene summarised the genotoxic potential in exposed humans:

> "There is no conclusive evidence to support that toluene is a genotoxic agent. Results from human occupational exposure studies are inconsistent, and are limited by small cohort size (15–45/group), lack of historical exposure monitoring, and (in some cases) concurrent exposure to other chemicals." (ATSDR, 2017).

The New Zealand EPA classifies benzene, methyl- as a 6.8B substance – a substance that is a suspected human reproductive or developmental toxicant (EPA, 2020).

The New Zealand EPA classifies benzene, methyl- as a 6.9B substance – a substance that is harmful to human target organs (EPA, 2020).

Animals

The AICIS review of toluene summarised the acute toxicity in experimental animals:

> "The chemical is of low acute toxicity from oral exposure in rats with a median lethal dose (**LD50**) of 2,600–7,500 g/kg bw [sic1] (WHO, 2004)."
>
> "The chemical is of low acute toxicity from dermal exposure with an LD50 in rabbits of 12,125 **mg/kg bw** (Registry of Toxic Effects of Chemical Substances)."
>
> "The chemical is of low acute toxicity from inhalation exposure, with **LC50** values in the range of 20,000–26,000 mg/m^3 for mice, and approximately 45,000 mg/m^3 for rats (IPCS, 1986). However, the chemical is known to cause central nervous system (**CNS**) toxicity immediately after exposure to high concentrations of the chemical by inhalation or ingestion (ATSDR, 2000; IPCS, 1986)." (References cited in AICIS, 2017).

The AICIS review of toluene summarised the irritation/corrosion potential in experimental animals:

> "Respiratory tract irritation, particularly in the nasal cavity, has been reported in animal studies with the chemical at concentrations of 600 ppm and greater. However, in lifetime and 28-day studies, no changes were seen in the nasal epithelium following exposure to concentrations of 300 ppm of the chemical (US EPA, 2005)."

"The chemical is a slight to moderate skin irritant in rabbits and guinea pigs (IPCS, 1986)."

"The chemical was a slight to severe irritant to the conjunctival membrane in rabbits (WHO, 1986). In the one study where severe irritation was seen, 2 mg was placed into the eye of a rabbit for 24 hours. Mild effects were seen in two studies where 870 **µg** and 100 mg were applied for 72 hours or 30 seconds respectively before the eyes were rinsed (WHO, 1986). In a more recent study (1995), the chemical produced slight irritation in the eyes of rabbits tested in accordance with good laboratory procedure (**GLP**) and **OECD TG** 405 (WHO, 2004)." (References cited AICIS, 2017).

The ATSDR review of toluene noted:

"Skin irritation can occur in humans and animals dermally exposed to toluene. In humans, this may be due to the degreasing action of toluene and its removal of protective skin oils. However, exposure to toluene vapors of 100–2,000 ppm for 95 days (pre-mating, mating, gestation, and lactation) in a multigenerational study had no effects on the skin in **F0** and **F1** parental rats or F1 and **F2** weanlings. Repeated or continuous contact with undiluted toluene in guinea pigs and mice leads to swelling, inflammatory cell infiltration, and increased epidermal thickness."

"Humans have reported eye irritation following exposure to toluene vapors at concentrations ≥ 100 ppm. This is probably the result of direct contact of toluene vapor with the outer surface of the eye and thus, is not a true systemic effect. Slight to moderately severe irritation of rabbit eyes has been reported following direct application of toluene to the conjunctiva. Reports of color vision deficits in occupationally exposed workers have been postulated to involve toluene interference with dopaminergic mechanisms of retinal cells or toxic demyelination of optic nerve fibers." (ATSDR, 2017).

The AICIS review of toluene summarised the sensitisation potential in experimental animals:

"The chemical did not cause skin sensitisation in a study using the guinea pig maximisation test (WHO, 2004)." (Reference cited in AICIS, 2017).

The ATSDR review of toluene summarised the repeat inhalation dose toxicity in experimental animals:

"Numerous studies in animals have also reported clinical signs of neurotoxicity and neurobehavioral alterations following acute, intermediate, or chronic inhalation exposure to toluene. Consistently reported effects following acute exposure include overt signs of neurotoxicity (ataxia, tremors, inability to walk); increased, followed by decreased, locomotor activity at ≥ 500 ppm; impaired learning and/or memory at 125–4,000 ppm; and impaired motor coordination and reflexes at ≥ 100 ppm. However, studies of rodents exposed for intermediate durations to concentrations as high as 1,000 ppm have not found strong and consistent evidence for exposure-related changes for these neurological end points. Following repeated abuse-like exposures (> 1,000 ppm), neurobehavioral alterations have been observed in several animal studies.

"Various other neurological effects have also been reported in animal inhalation studies. Hearing loss in animals has been observed following acute-and intermediate-duration exposure to toluene at concentrations of ≥ 250 ppm in

guinea pigs and ≥ 1,000 ppm in rats. Observed hearing loss may not be solely due to neurological damage, as animal studies indicate that exposure to 500–2,000 ppm damages the cells in the inner ear (cochlea) that are responsible for amplifying incoming sound waves prior to initiation of the nerve signal from the ear to the brain. Other effects that have been reported include alterations in visual-evoked brain potentials (**VEP**s) or electroretinograms (**ERG**s), altered pain perception, decreased olfactory sensitivity, altered sleep patterns, altered brain weight and volume in rats, altered levels of glial fibrillary acidic protein (**GFAP**) and markers of oxidative stress, and altered levels of neurotransmitters, precursors, and receptors." (References cited in ATSDR, 2017).

The ATSDR review of toluene noted:

"Evidence from a few animal studies suggests that repeated exposure to toluene can suppress the immune system, although current data from human studies are limited and inconclusive. Various reports indicate hepatic and renal effects following inhalation and oral exposure to toluene; however, there is little support for irreversible damage to the liver or kidney." (ATSDR, 2017).

The ATSDR review of toluene summarised the reproductive toxicity in experimental animals:

"A few studies in animals exposed to toluene via inhalation at concentrations ≥ 2,000 ppm reported effects on male and female reproductive tissues, including abundant vacuoles, lytic areas, and mitochondrial degeneration in the antral follicles of the ovaries of female rats and reduced sperm count, motility, and quality and altered reproductive organ weight and histology in male rats. However, changes in sperm count and epididymis weight were not accompanied by any change in indices of reproductive performance (for example, fertility) in male rats exposed to 2,000 ppm for 60 days before mating. The majority of animal studies provide little evidence for toluene reproductive toxicity. Studies in rats exposed repeatedly by inhalation to toluene, including a 2-generation reproductive toxicity study, have shown no evidence of adverse effects on mating or fertility at tested concentrations as high as 1,200–2,000 ppm. In addition, the majority of numerous gestational exposure studies in rodents reported no exposure-related changes in reproductive indices." (ATSDR, 2017).

The ATSDR review of toluene summarised the developmental toxicity in experimental animals:

"Experiments with pregnant mice demonstrated that 10-minute exposures to 2,000 ppm resulted in low uptake of toluene into fetal tissue and suggest that, at lower exposure levels, absorbed toluene is preferentially distributed to maternal adipose tissue before distribution to the developing fetus.

"A number of developmental toxicity studies with rats, mice, and rabbits involving toluene exposure by inhalation during gestation have been conducted to further describe developmentally toxic effects from toluene and exposure-response relationships. The results indicate that toluene did not cause maternal or developmental toxic effects in animals at exposure levels < 1,000 ppm administered for 6–7 hours/day during gestation. Predominant effects reported at concentrations ranging from 1,000 to 3,000 ppm include retarded fetal growth and skeletal development and altered development of behavior in offspring; these effects were almost always accompanied by signs

of maternal toxicity. Other animal studies reported that continuous, 24-hour/day exposure during gestation caused maternal body weight depression and effects on fetuses including depressed body weight and delayed skeletal ossification at toluene concentrations as low as 133–399 ppm in rats, mice, and rabbits. Impaired learning and memory, increased malformations, and fetal death have been observed when animals were exposed during gestation to higher concentrations modeling solvent abuse (8,000–16,000 ppm, 15–30 minutes/day)." (ATSDR, 2017).

The ATSDR review of toluene summarised genotoxic potential in experimental animals and *in vitro* test systems:

"Most short-term *in vivo* tests in laboratory animals have not found genotoxic effects. Similarly, genotoxic effects were not induced in the majority of *in vitro* assays." (ATSDR, 2017).

4.2 Cancer

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

There is *inadequate evidence* in humans for the carcinogenicity of toluene.

There is e*vidence suggesting lack of carcinogenicity* of toluene in experimental animals.

With an overall evaluation that:

Toluene is *not classifiable as to its carcinogenicity to humans (Group 3)* (IARC, 1999).

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

The New Zealand EPA has not classified benzene, methyl- as a 6.7A or 6.7B substance – a substance that is a known or presumed, or a suspected human carcinogen, respectively (EPA, 2020).

Humans

The ATSDR review of toluene summarised the data on exposure and carcinogenicity in humans:

"Human and animal studies generally do not support a concern for the carcinogenicity of toluene. Numerous human epidemiology studies were located that assessed toluene exposure as a possible risk factor for cancer. Five of the studies examined workers exposed predominantly to toluene, whereas the remainder of the human studies primarily involved subjects exposed to mixtures of solvents including toluene. Cancers of most sites were not significantly associated with toluene exposure, and there was weak consistency in the findings of those studies that did find association of a particular cancer type with toluene exposure. The information from these studies is inadequate to assess the carcinogenic potential of toluene,

predominantly because of the lack of consistent findings across the studies and the likelihood that many of the studied groups were exposed to multiple chemicals." (ATSDR, 2017).

Animals

The ATSDR review of toluene summarised the data on exposure and carcinogenicity in experimental animals:

"The validated animal inhalation bioassays were negative; however, one available oral study showed a nondose-related increase in a variety of tumors. Dermally administered toluene markedly inhibits skin tumorigenesis in the two-stage mouse model utilizing phorbol-12-myristate-13-acetate (**PMA**) as a promoter. The reduction in tumorigenesis was observed in mice initiated with dermal applications of benzo(a)pyrene or 7,12-dimethylbenz(a) anthracene. Thus, the data do [sic] not support a firm conclusion regarding the carcinogenicity of toluene." (ATSDR, 2017).

4.3 Absorption, distribution, metabolism and excretion

The ATSDR review of toluene summarised the absorption, distribution, metabolism and excretion (**ADME**):

"Studies with volunteers and laboratory animals indicate that toluene is rapidly absorbed from the respiratory tract with less rapid absorption occurring in the gastrointestinal tract and skin (Bushnell *et al*. 2007; Nadeau *et al*. 2006; Pyykko *et al*. 1977; Sullivan and Conolly 1988; Thrall and Woodstock 2002; Thrall *et al*. 2002a). Studies with animals exposed by inhalation or oral routes showed that absorbed toluene is distributed widely to tissues throughout the body with preferential distribution to adipose tissue, brain, bone marrow, liver, and kidney. Absorbed toluene is distributed in pregnant animals, as well as to the developing fetus. The primary initial steps in toluene metabolism in humans and laboratory animals are side-chain hydroxylation (to form benzyl alcohol) catalyzed predominantly by the cytochrome P450 (**CYP**) isozyme, **CYP2E1** (Nakajima and Wang 1994; Nakajima *et al*. 1991, 1992a, 1992b, 1993, 1997; Tassaneeyakul *et al*. 1996) followed by oxidation to benzoic acid. Most of the benzoic acid is then conjugated with glycine to form hippuric acid, but a small portion can be conjugated with **UDP**-glucuronate to form the acyl-glucuronide. Studies with volunteers and human liver microsomes indicate that a very small portion (< 1–5%) of absorbed toluene can be converted by **CYP1A2**, **CYP2B2**, or CYP2E1 to *ortho*-or *para*-cresol, which are excreted in the urine as sulfate or glucuronate conjugates (Baelum *et al*. 1993; Nakajima *et al*. 1997; Tassaneeyakul *et al*. 1996). In both humans and rats, up to about 75–80% of inhaled toluene that is absorbed can be accounted for as hippuric acid in the urine (Lof *et al*. 1993; Wang and Nakajima 1992). Remaining absorbed toluene is excreted unchanged in exhaled air and urine and as conjugates of minor metabolites in urine (Ducos *et al*. 2008; Janasik *et al*. 2008, 2010; Lof *et al*. 1993; Ogata 1984; Pierce *et al*. 2002; Tardif *et al*. 1998). Analyses of kinetic data for toluene concentrations in blood, exhaled breath, adipose tissue, or urine following inhalation exposure of humans indicate that most absorbed toluene is rapidly eliminated from the body and that a smaller portion (that which gets into adipose tissues) is slowly eliminated (Janisik *et al*. 2008; Leung and Paustenbach 1988; Lof *et al*. 1993; Nise *et al*. 1989; Pellizzari *et al*. 1992; Pierce *et al*. 1996, 1999, 2002). For example, elimination kinetics for toluene-exposed workers have been described by a three-phase elimination

model with half-times of 9 minutes, 2 hours, and 90 hours for toluene in blood and a single median elimination half-time of 79 hours for toluene in fat (Nise *et al*. 1989). In a study of volunteers exposed by inhalation to about 50 ppm for 4 hours, a two-phase decline of urinary toluene concentration was observed with half-lives of 0.88 and 12.9 hours (Janisik *et al*. 2008)." (References cited in ATSDR, 2017).

The ATSDR review of toluene noted for dermal absorption:

"Results from early studies indicated that toluene is absorbed slowly through human skin (Dutkiewicz and Tyras 1968). The rate of absorption of toluene in human forearm skin was found to range from 14 to 23 **mg/cm²/hour**. EPA (1992b) estimated a human dermal permeability coefficient, **Kp**, of **1 cm/hour**, based on these data. Based on these estimates, Brown *et al*. (1984) calculated that bathing in water containing 0.005–0.5 mg toluene/L (15 minutes/day) would result in absorbed dermal dose ranges of 0.0002–0.02 **mg/kg/day** for a 70 kg adult and 0.0004–0.04 mg/kg/day for a 10.5 kg infant. Transdermal uptake of toluene directly from the air is expected to be low, accounting for 1–2% of the total body burden received following exposure to toluene vapors (Brooke *et al*. 1998; Weschler and Nazaroff, 2014)." (References cited in ATSDR, 2017).

The ATSDR review of toluene summarised possible mechanisms of toxicity:

"Dysfunction of the central nervous system is a critical human health concern following acute, intermediate, or chronic inhalation exposure to toluene. Therefore, the mechanisms of toluene toxicity have been investigated predominately in the nervous system. Proposed mechanisms of toxicity include altered membrane and membrane channel properties; direct damage to brain structures via lipid damage, oxidative stress, and/or apoptosis; altered neurotransmitter synthesis, release, degradation, and receptor binding; disruption of the hypothalamic-pituitary-adrenal axis; and neuroinflammation."

"Mechanistic studies in other systems are limited, but suggested mechanisms are similar to those observed for neurotoxicity, including altered membrane properties, apoptosis, oxidative stress, and gene expression alterations." (ATSDR, 2017).

The ATSDR review of toluene noted for potential susceptible populations:

"Environmental or genetic factors that decrease the capacity for metabolic detoxification of toluene are likely to increase susceptibility. This is supported by experiments in which inhibiting or enhancing toluene metabolism via CYP 2E1 respectively enhanced or inhibited toluene-induced hearing loss in rats (Campo *et al*. 1998, 2008; Pryor *et al*. 1991). Chronic consumers of alcohol, and users of any medication that interfered with toluene metabolism, would be likely to have an increased risk for this reason. Additionally, smokers may have an increased risk of toxicity due to a possible repression of CYP 2E1 via epigenetic modifications (Jimenez-Garza *et al*. 2015). Differences in the relative efficiency of enzymes found in ethnic populations may lead to differences in toluene susceptibility, as ethnic variations in the occurrence of CYP isozymes, alcohol dehydrogenase, and aldehyde dehydrogenase are known to exist (Kawamoto *et al*. 1995, 1996; Kim *et al*. 1997, 2015)." (References cited in ATSDR, 2017).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows toluene 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	50	191	150	574
Austria	50	190	100	380
Belgium[1]	20	77	100[2]	384[2]
Canada – Ontario	20			
Canada – Québec	50	188		
Denmark	25	94	50	188
European Union[3]	50	192	100[2]	384[2]
Finland	25	81	100[2]	380[2]
France[4]	20	76.8	100[2]	384[2]
Germany – **AGS**	50	190	200[2]	760[2]
Germany – **DFG**	50	190	200[2]	760[2]
Hungary		190		380
Ireland	50	192	100[5]	384[5]
Israel	50	188		
Italy[6]	50	192		
Japan – **MHLW**	20			
Japan – **JSOH**	50	188		
Latvia	14	50	40[2]	150[2]
New Zealand	50	188		
People's Republic of China		50		100[2]
Poland		100		200
Romania	50	192	100[2]	384[2]
Singapore	50	188		
South Korea	50	188	150	560
Spain[6]	50	192	100	384
Sweden	50	192	100[2]	384[2]
Switzerland	50	190	200	760
The Netherlands		150		384
Turkey	50	192	100[2]	384[2]
USA – **NIOSH**	100	375	150[2]	560[2]
USA – **OSHA**	200		300	
UK	50	191	100	384

TABLE 3: Exposure standards for toluene 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] 15 minutes average value.

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

[4] Restrictive statutory limit values.

[5] 15 minutes reference period.

[6] **skin** notation.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on toluene were **ECHA**, **ANSES**, ACGIH®, DFG and **SCOEL**.

5.2 ECHA

The European Chemicals Agency (ECHA) evaluation of toluene noted that the basis of the long-term inhalation Derived Non-Effect Level (**DNEL**) was a **NOAEC** for development and fertility effects from animal reproductive toxicity studies (600 ppm; 2,250 mg/m^3) and a **LOAEC** for abortions from human studies (88 ppm; 330 mg/m^3) (ECHA, 2013), and while dermal absorption of liquid toluene could occur, dermal absorption of toluene vapour was expected not to be significant (ECHA, 2013).

The ECHA review noted that minimal Margins of Safety (**MOS**) should be applied to these NOAEC/LOAEC to derive DNELs: 30 for the animal NOAEC; and, 5 for the human LOEAC, giving reference values of respectively 20 ppm and 17.6 ppm (ECHA, 2013).

5.3 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 toluene concluded that an 8h-**OEL** of 20 ppm (75.4 mg/m^3) and a **STEL** of 100 ppm (377 mg/m^3) could be recommended (ANSES, 2008).

Rationale:

> "This recommendation aims at preventing potential effects in the workplace leading to visual impairment such as color discrimination. This value is set based on the results of two studies (Cavalleri *et al*. 2000; Campagna *et al*. 2001) which indicate that the Lowest Observed Adverse Effect Level (**LOAEL**) could be observed in humans from an exposure of 40 ppm or 150.8 mg/m^3.
>
> "Furthermore, the OEL committee recommends setting a STEL of 100 ppm (or 377 mg/m^3) in order to limit peaks in exposure and thus to prevent potential short-term neurobehavioural effects. This value is identical to the value of 100 ppm recommended by SCOEL in 2001. The relevance of this European value was furthermore reaffirmed by the publication, in 2005, of an experimental study on humans (Lammers *et al*. 2005).
>
> "The OEL committee recommends retaining the 'skin' notation for toluene as some occupational scenarios could lead to skin exposure to liquid toluene, during which skin penetration is likely to substantially contribute to an increase in body burden." (References cited in ANSES, 2008).

5.4 ACGIH®

The ACGIH® review of toluene concluded with recommendations that a **TLV-TWA** of 20 ppm [75 mg/m^3] for occupational exposure to toluene, would minimise the potential for subclinical changes in blue-yellow colour vision, and for spontaneous abortion in female workers (ACGIH®, 2007).

Rationale:

> "Color vision changes have been reported in a longitudinal study of a population of rotogravure printers in France where personal air sampling in the breathing zone showed an average of 36 ppm at the time of the tests were administered in early 1993 (Campagna *et al*., 2001). These workers had an average duration of employment of 18 years during which time the toluene exposures were continuously reduced. Workers in a rubber production plant also had color vision changes with an estimated exposure at the time of measurement of 42 ppm (Cavalleri *et al*., 2000). Based on the subclinical nature of the changes and the uncertainty about past higher exposure levels in these studies, 20 ppm is expected to be protective against impairment of color vision. Spontaneous abortions as determined by a reproductive questionnaire administered by a personal interview were found in 55 women who were exposed at 88 ppm toluene (range, 50–150 ppm) in an audio speaker factory (Ng *et al*., 1992). The rate of spontaneous abortion was 2.8 times higher than the community reference group. In reproductive studies in rats, toluene did not induce adverse effects on fertility of reproductive performance at 500ppm (Roberts *et al*., 2003). A TLV-TWA of 20 ppm is expected to be protective of spontaneous abortions. Toluene is not assigned a **Skin** notation based on studies that show low absorption. NTP (1990) concluded that there was no evidence of carcinogenic activity in rats or mice inhaling up to 1,200 ppm toluene for their lifetimes. Toluene has been assigned an A4, Not Classifiable as a Human Carcinogen, notation. There is no information upon which to assign a **SEN** notation or recommend a **TLV-STEL**." (ACGIH®, 2007).

The ACGIH® noted that **BEI**s® had been recommended for toluene (ACGIH®, 2007).

5.5 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] re-evaluation of toluene (DFG, 1996) concluded:

> "The **MAK** value for toluene was established in 1985 at 100 **ml/m³**. However, when the results described above from more recent behavioural toxicology studies are used as criteria in the assessment, it is no longer possible to maintain that a toluene concentration of 100 ml/m³ has no adverse effects on health. The data from performance studies suggest that first effects are found at concentrations of about 75 ml/m³ (LOAEL); this applies for short-term effects (Echeverria *et al*. 1989) and long-term effects (Foo *et al*. 1990). The findings of Oerbaek and Nise (1989) at levels below 50 ml/m³ which are considered significant in the documentation of the EC scientific group are not taken into account in the establishment of this threshold. The higher toluene concentrations to which those printers had been exposed in the long term were not assessed individually. In this context, the absence of reproducible effects found in repeated performance tests with persons exposed long-term to higher concentrations (62 ml/m³) in spite of simultaneous noise exposure (Kempe *et al*. 1980) must be taken into account. The data available for subjective effects of toluene (effects on how the persons feel) suggest that the LOAEL is about 60 ml/m³. Once more, the findings of Oerbaek and Nise (1989) are not taken into account here whereas the results of the repeated tests of Kempe *et al*. (1980) with persons exposed under conditions which were probably similar to those of the collective studied by Oerbaek and Nise are considered to document the LOAEL.

"If it is assumed that the effects described for low level exposures are reversible after the end of exposure, then persistent behavioural toxic effects are not to be expected after exposure to toluene concentrations of 50 ml/m³, that is, adverse effects on performance and on how the persons feel will not occur. The MAK value for toluene was therefore established in 1993 at 50 ml/m³.

"Since recent studies have demonstrated that toluene does not penetrate the skin in toxic amounts during normal handling, special designation of the substance is not necessary.

"Because the half-life of toluene in the organism is between 2 hours and shift length, the substance is included in category II, 2 for the limitation of exposure peaks (peak level 5 times the MAK value, maximum peak duration 30 minutes, not more than twice per shift).

"The prenatal toxicity of very high toluene concentrations has been documented for several animal species and for man. Malformations indicative of specific teratogenicity, however, were not found. The prenatal toxicity took the form of embryonal death or delayed foetal growth and delayed skeletal system development, depending on the exposure concentration. Permanent damage of children was seen only when their mothers had suffered from chronic toluene intoxication as a result of sniffing toluene or paints or lacquers containing toluene. Since the toluene concentrations involved in these cases are unknown, these data for effects in man cannot be used for quantitative evaluation. This also applies for the four epidemiological studies described above. The studies of McDonald *et al*. and Huang involve exposure to mixtures without details of the exposure concentrations. The Singapore study (Ng *et al*.) which suggests that toluene concentrations in the range between 50 ml/m³ and 150 ml/m³ could have abortive effects is surprising from two points of view. Even after exposure to demonstrably high concentrations, abortive effects have not been described to date; authors reporting the effects on women who had inhaled high concentrations during toluene abuse all agree that the substance did not cause embryonal deaths but delayed growth and possibly teratogenic effects. In addition, evidence of abortive effects has not been seen in any of the animal species tested according to present-day standards, in the mouse, rat or rabbit. Thus, the only reproductive toxicity studies which are suitable for the determination of the **$NOAEL_D$** are the inhalation studies with these three animal species.

"The available data demonstrate clearly that the $NOAEL_D$ values for the mouse, rat and rabbit are 400, 750 and 500 ml/m³; a concentration higher than 400 ml/m³ has not yet been tested in the mouse [sic] in studies which meet GLP standards. Therefore it seems to be reasonable to determine the mean of the three $NOAEL_D$ values and to base the threshold limit on this average of 550 ml/m³. Since there are no significant metabolic differences between man and these experimental animals it may be concluded that, provided the MAK value of 50 ml/m³ is observed, prenatal toxic effects are not to be expected. Toluene is therefore classified in **pregnancy risk group C**." (References cited in DFG, 1996).

The DFG MAK re-evaluation of toluene (2002) confirmed the MAK value, based on updated data, but revised the **Peak limitation category** to 2; excursion factor, 4 (DFG, 2002).

5.6 SCOEL

The EC Scientific Committee on Occupational Exposure Limits (SCOEL) review of toluene recommended an 8-hour TWA of 50 ppm (192 mg/m^3) and a 15-minute STEL of 100 ppm (384 mg/m^3), with a 'skin' notation (SCOEL, 2001).

Rationale:

> "The data from performance studies suggest that the first effects (LOAEL) are found at concentrations of about 75 ppm (237 mg/m^3); this applies for short-term effects (Echeverria *et al*., 1989) and long-term effects (Foo *et al*., 1990). Ørbaek and Nise (1989) reported about first effects at levels below 50 ppm (191 mg/m^3). However, the higher toluene concentrations to which those printers had been exposed in the long term had not been assessed individually. In this context, the absence of reproducible effects found in repeated performance tests with persons exposed long-term to higher concentrations (62 ppm – 237 mg/m^3) in spite of simultaneous noise exposure (Kempe *et al*., 1980) must be taken into account. The data available for subjective effects of toluene (effects on how the persons feel) suggest that the LOAEL is about 60 ppm (230 mg/m^3).
>
> "Overall, a great deal of human data is available, which produce no reliable evidence of effects at or below toluene concentrations of 50 ppm (192 mg/m^3). Therefore the SCOEL considers 50 ppm (192 mg/m^3) to be an appropriate level for the 8 hour TWA.
>
> "A STEL (15 min) [sic] of 100 ppm (384 mg/m^3) is proposed to limit peaks of exposure which could result in short-term neurobehavioural effects. This is based on the toxicokinetics of toluene, in conjunction with the experimental data by Iregren *et al*. (1986) on human neurobehaviour at 80 ppm toluene. According to Arlien-Søborg (1992) the steady-state level of toluene in blood is reached after ≈ 25 min of exposure. This means that a 15 min peak exposure of toluene, at the proposed STEL, would not lead to adverse health effects.
>
> "A 'skin' notation is also recommended, as dermal absorption of liquid toluene could contribute substantially to the total body burden." (References cited in SCOEL, 2001).

6.0 Analytical methods for the assessment of airborne toluene

A common method to measure toluene exposure is using NIOSH Method 1501, Issue 3 (NIOSH, 2003).

Using this method an air sample of 1 to 8 litres is collected onto a coconut shell charcoal sorbent tube, using a flow rate of up 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.

This method can achieve a limit of detection of 0.7µg per sample, allowing reliable detection of airborne toluene at concentrations below the proposed WES-TWA and WES-STEL values.

7.0
Discussion

WorkSafe's WES for toluene has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates that toluene is locally and systemically toxic to humans, causing irritation, neurotoxicity and increased incidences of abortion. Toluene is locally and systemically toxic to experimental animals, causing irritation, neurotoxicity, reproductive and developmental effects.

Based on the aforementioned documentation, informed by the conclusions of the ECHA, ANSES, ACGIH®, DFG and SCOEL, reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 50 ppm (188 mg/m³) for toluene, to be inadequate to manage health risks from possible workplace exposure:

- Toluene is a potential neurological toxicant and abortifacient in exposed workers (ECHA, 2013; ANSES, 2008; ACGIH®, 2007).
- The ECHA review of toluene recommended a long-term inhalation DNEL of 20 ppm, based on a NOAEC for development and fertility effects from animal reproductive toxicity studies (600 ppm; 2,250 mg/m³) and a LOAEC for abortions from human studies (88 ppm; 330 mg/m³) (ECHA, 2013), with minimal Margins of Safety of 30 for the animal NOAEC; and, 5 for the human LOEAC, giving reference values of respectively 20 ppm and 17.6 ppm (ECHA, 2013).
- The ANSES review of toluene recommended an 8-hour OEL of 20 ppm (75.4 mg/m³) to be protective against visual impairment in humans (LOAEL of 40 ppm; 150.8 mg/m³; Cavalleri *et al*. 2000; Campagna *et al*. 2001 cited in ANSES, 2008); and, a 15-min STEL of 100 ppm (377 mg/m³) to be protective against other neurobehavioural effects (Lammers *et al*., 2005 cited in ANSES, 2008), with a skin notation.
- The ACGIH® review of toluene concluded with recommendations that a TLV-TWA of 20 ppm [75 mg/m³] would minimise the potential for subclinical changes in blue-yellow colour vision, and for spontaneous abortion in female workers (ACGIH®, 2007).
- The DFG review of toluene confirmed a MAK value of 50 ppm (190 mg/m³), and confirmed the Pregnancy Risk Group C assignment and "**H**" notation (DFG, 2014). The MAK value was based on adverse neurobehavioural effects with a LOAEL of 60 ppm (DFG, 1996).
- The SCOEL review of toluene recommended an 8-hour TWA OEL of 50 ppm (192 mg/m³), with a 15-minute STEL of 100 ppm (384 mg/m³) to be protective against neurobehavioural effects (SCOEL, 2001).
- The proposed WES-TWA of 20 ppm (75 mg/m³) for toluene is intended to protect exposed workers from potential neurotoxicity, and abortion in female workers. It is noted that the proposed WES-TWA of 20 ppm may not be protective for individuals with increased sensitivity to chemicals (ATSDR, 2017) or with genetic factors that limit the effectiveness of key detoxification enzymes (ATSDR, 2017).

- The proposed WES-STEL of 100 ppm for toluene is intended to protect exposed workers from potential neurotoxicity, based on the NOAEL of 110 ppm (Lammers *et al*., 2005 cited in ANSES, 2008).
- A ***skin*** notation is justified for toluene, due to the reported significance of dermal absorption from contact with liquid toluene (ANSES, 2008). Biological monitoring of workers is recommended to assess total exposures to toluene and potential health risks.
- Available information indicates that toluene is not a sensitiser (ACGIH®, 2007), and a ***sen*** notation is not warranted.
- Toluene is a known ototoxin (ATSDR, 2017).

8.0
Recommendations

WorkSafe considers its current WES-TWA of 50 ppm (188 mg/m^3) for toluene 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 toluene of 20 ppm (75 mg/m^3)
2. adopt a WES-STEL for toluene of 100 ppm (384 mg/m^3)
3. maintain a *skin* notation for toluene
4. adopt an ***oto*** notation for toluene.

Noting that the proposed WES-TWA and WES-STEL for toluene may not eliminate all risk, due to the potential contribution of dermal exposures from liquid toluene to total body burden, and for individuals with known environmental or genetic sensitivities, 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].
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
BEI®	Biological Exposure Indices – an ACGIH® term.
BTEX	Benzene-toluene-ethylbenzene-xylene.
cm/hr	Centimetre per hour.
CNS	Central nervous system.
CYP	Cytochrome P450.
CYP1A2	Cytochrome P450 family 2; subfamily A; member 2.
CYP2B2	Cytochrome P450 family 2; subfamily B; member 2.
CYP2E1	Cytochrome P450 family 2; subfamily E; member 1.
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.
DNEL	Derived No Effect Level.
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
ERG	Electroretinogram.
F0	Parents to first filial generation, F1.
F1	First filial generation.
F2	Second filial generation.
GFAP	Glial fibrillary acidic protein.
GLP	Good Laboratory Practice.
"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.

TERM	MEANING
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.
Kp	Dermal permeability coefficient.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LOAEC	Lowest Observed Adverse Effect Concentration.
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 (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. Values set by the DFG.
µg	Microgram or one millionth of a gram.
mg	Milligram or one thousandth of a gram.
$mg/cm^2/hr$ or $mg/cm^2.hr$	Milligrams of substance per square centimetre per hour [rate of skin absorption by area of skin exposed].
mg/kg	Milligrams per kilogram.
mg/kg b.w. or mg/kg bw	Milligram of substance per kilogram body weight.
mg/kg/day	Milligrams per kilogram per day.
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 or ml/m^3	Millilitres of substance per cubic metre of air; equivalent toppm.
MOS	Margin of Safety.
MRL	Minimal Risk 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.
NOAEL	Developmental No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Limit (equivalent to a WES).

TERM	MEANING
OSHA	Occupational Safety and Health Administration, US Department of Labor.
oto	Ototoxic. The substance may alone, or in concert with noise, result in hearing loss.
Peak limitation category 2/II	Substances with systemic effects; Excursion factor = 2 [default]; Duration 15 minutes, average value; Number per shift = 4; Interval = 1 hour. A DFG term.
PMA	Phorbol-12-myristate-13-acetate.
ppm	Parts of vapour or gas per million parts of air.
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.
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.
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.
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.
TG	Test Guideline. An OECD 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 workday, 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.
US EPA	United States Environmental Protection Agency.
VEP	Visual-evoked brain potential.
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.

TERM	MEANING
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.
WHO	World Health Organisation, Geneva.

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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