Workplace Exposure Standard (WES) review

1,4-DIOXANE
(CAS NO: 123-91-1)

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New Zealand Government

WORKSAFE
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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for 1,4-dioxane should be changed.

The WES review considers the potential for exposures to 1,4-dioxane in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposure.

The review includes a recommendation to change the WorkSafe WES for 1,4-dioxane, which is currently set at a **WES-TWA** of 25**ppm** [90**mg/m³**] for **inhalable fraction** with a ***skin*** *notation*, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: Diethylene dioxide; diethylene ether; *p*-dioxane; glycol ethlyene ether.

2.0 Chemical and physical properties

1,4-Dioxane is a clear, colourless, flammable liquid with a faint ethereal odour at room temperature (**US EPA**, 2017; **NTP RoC**, 2016; **DECOS**, 2015; **ACGIH®**, 2001).

The odour threshold for 1,4-dioxane is reported to be 2.8 to 5.7ppm or 6.5 to 9.8mg/m^3 (**NICNAS**, 1998; ACGIH®, 2001).

The NICNAS review noted that 1,4-dioxane is hygroscopic and reacts with water in the presence of air to form explosive peroxides (NICNAS, 1998).

Chemical and physical properties 1,4-dioxane include:

Molecular weight	88.1g/mol
Formula	$C_4H_8O_2$
Specific gravity	1.036 at 20°C
Melting point	11.8°C
Boiling point	101.1°C at 760mm Hg
Vapour pressure	3.9kPa at 20°C; 4.9kPa at 25°C
Relative vapour density [air = 1]	3.03
Flash point	Closed cup: 12°C; Open cup: 23°C
Explosive limits	Lower: 2% v/v; Upper: 22% v/v
Auto-ignition	180°C
Log KOW	-0.27 to -0.49
Solubility	Water: >800g/L; miscible with most organic solvents
Decomposition products	Carbon monoxide may be released in a fire
Conversion factors	1mg/m^3 = 0.28ppm 1ppm = 3.60mg/m^3

US EPA, 2017; DECOS, 2015; NICNAS, 1998; ACGIH®, 2001

TABLE 1: Physicochemical properties of 1,4-dioxane

Health-related hazard classifications for 1,4-dioxane:

	HSNO CLASSIFICATION
Substance	1,4-Dioxane
CAS No.	123-91-1
Classification	6.1D (All); 6.1D (O); 6.3B; 6.4A; 6.7A; 6.9B (All); 6.9B (O); 6.9B (I)

TABLE 2:
HSNO health-related hazard classifications of 1,4-dioxane (**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] Dermal exposure route.
[I] Inhalation exposure route.

3.0
Uses

1,4-Dioxane is widely used as a solvent, a wetting-dispersing agent, a degreasing agent, and as a component in a range of products in various industries (NTP RoC, 2016; DECOS, 2015).

Other uses of 1,4-dioxane include as a chemical intermediate and a polymerisation catalyst (NTP RoC, 2016).

1,4-dioxane may also be produced as a reaction by-product, particularly in chemicals produced by ethoxylation, and remain as a contaminant (US EPA, 2017).

Occupational exposure to 1,4-dioxane can occur during production, storage, transportation and end-use.

Workers can be exposed to 1,4-dioxane via inhalation and eye or dermal contact (NTP RoC, 2016).

The number of workers exposed or potentially exposed to 1,4-dioxane in New Zealand workplaces is unknown.

Statistics New Zealand 2018 data indicate that 19,000 New Zealand workers were working in the areas of:

- basic chemical and chemical product manufacturing
- polymer product manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

4.2 Cancer

4.3 Absorption, distribution, metabolism and excretion

4.1 Non-cancer

Humans

The **ATSDR** toxicology profile of 1,4-dioxane noted that:

> "Several cases of death in humans have been documented after exposure to high concentrations of 1,4-dioxane. Barber (1934) described five deaths that occurred within a period of 2 weeks among factory workers engaged in a process that involved primarily exposure to 1,4-dioxane vapors, although minimal dermal exposure could not have been avoided. Three of the subjects suffered from abdominal pain and vomiting before death occurred. Post-mortem examination of the subjects showed extensive gross and microscopic lesions to the liver and kidneys. Based on his observations, Barber (1934) suggested that the effects on the kidneys may have been responsible for the fatal outcome and that liver necrosis, although widespread, was compatible with recovery. No exposure levels were available in these case reports. Johnstone (1959) described an additional fatal case of a worker exposed to 1,4-dioxane for only 1 week and whose post-mortem examination showed kidney and liver alterations similar to those described by Barber (1934). In the Johnstone case, the room in which the patient had worked had no exhaust ventilation and the worker was not provided a respirator. The minimum concentration of 1,4-dioxane in the room was 208ppm and the maximum was in excess of 650ppm; the average concentration was 470ppm. In addition, dermal exposure may have been considerable in this case." (References cited in ATSDR, 2012).

The New Zealand EPA classifies 1,4-dioxane as a 6.1D substance – a substance that is acutely toxic (EPA, 2019).

The DECOS recommendation on 1,4-dioxane summarised the irritation/corrosion potential in humans:

> "At concentrations 1,000mg/m^3 irritation of eyes, nose and throat was reported (**SCOEL**: European Commission 2002). Young *et al*. (1977) reported in 4 healthy volunteers during an inhalation study (exposure over 6 hours) irritation of the eyes at 50ppm (180mg/m^3); eye irritation was a frequent complaint throughout the exposure. Perception of the odour of dioxane diminished with time. Two of the subjects could not perceive the odour after 4 and 5hr in the chamber, whereas the other two subjects could still detect the odour at the end of the exposure period. The subject who first lost the ability to perceive the odour of dioxane also had the highest blood plasma concentration of dioxane. No other symptoms or complaints were recorded in this study (SCOEL Young *et al*.)." (References cited in DECOS, 2011).

The New Zealand EPA classifies 1,4-dioxane as a 6.3B and 6.4A substance – a substance that is mildly irritating to the skin and irritating to the eye, respectively (EPA, 2019).

The DECOS recommendation on 1,4-dioxane summarised the sensitisation potential in humans:

> "Inflammatory skin changes, showing symptoms of eczema, in the upper extremities and the face were seen after dermal exposure to 1,4-dioxane for several weeks in a 47-year-old female laboratory technician (SCOEL Sonneck 1964). A positive human patch-test is reported in a man who developed dermatitis after daily dipping in a 1,4-dioxane containing solvent (SCOEL Fregert 1974)." (References cited in DECOS, 2011).

The SCOEL recommendation on 1,4-dioxane summarised the repeated dose toxicity in humans:

> "In one case report a 21-year-old worker had been exposed to 1,4-dioxane for one week at concentrations ranging from 720mg/m^3 to 2340mg/m^3 [202ppm to 655ppm] . Moreover, he had repeatedly dipped his hands into a tub containing liquid 1,4-dioxane. The man had been an alcoholic. The signs experienced included pain in the upper abdomen, hypertonia and neurological symptoms. After one week of hospitalization the man died of kidney failure. Necropsy included renal cortex necrosis with severe interstitial haemorrhages. Severe centrilobular necrosis was found in the liver. The brain showed signs of demyelination and partial loss of nerve fibre tissue (Johnstone, 1959). Similar symptoms were observed in five patients who died after 1,4-dioxane exposure (Barber, 1934)." (References cited in SCOEL, 2004).

The New Zealand EPA classifies 1,4-dioxane as a 6.9B substance – a substance that is harmful to human target organs or systems (EPA, 2019).

The NICNAS review of 1,4-dioxane summarised the reproductive/developmental toxicity in humans:

> "Studies on 'reproductive outcome' were conducted in pregnant women (314 workers) exposed to chemicals (including 1,4-dioxane) in the electronics industry (Ailamazian, 1990). Effects included an increased incidence of miscarriages, premature births, maternal toxicosis, foetal ossifications and decreased birth weights. Gonadotoxic effects, associated with 1,4-dioxane exposure, also in the electronics industry, were reported by Mikheev *et al*. (1979). Insufficient data were available in these studies to draw any conclusions with respect to 1,4-dioxane exposure and the effects observed. A **PBPK** model, developed for lactating women, indicated that exposure to 25ppm 1,4- dioxane in air may give rise to a significant lactational transfer (Fisher *et al* 1997)." (References cited in NICNAS, 1998).

Animals

The DECOS recommendation on 1,4-dioxane summarised the acute toxicity in experimental animals:

> "The dermal **LD_{50}** was reported to be 7,855**mg/kg bw** for the rabbit. No toxic effects were mentioned.
>
> "With respect to inhalation the **LC_{50}** was 46,000–52,000mg/m^3 [12,880-14,560ppm] for rats and 36,700mg/m^3 [10,276ppm] for mice. Rats showed dyspnoea, apathy, narcosis, irritation of mucous membranes (eyes, respiratory tract), eyelid-reflex loss, unkempt coat, staggering and heart dilatation and after necropsy haemorrhagic erosion of the mucous membranes of the stomach and bloody contents in stomach and intestines (SCOEL BASF AG 1980).
>
> "Acute neurotropic effects of 1,4-dioxane were investigated. Depression of tonic extension after electroshock in rats was seen at concentrations ≥6,800mg/m^3 [>1,904ppm] and an oral administration of 1,050mg/kg bw caused a decrease in dopamine and serotonin levels in the hypothalamus and a decrease in serotonin in the medulla oblongata (SCOEL Frantik *et al*. 1994)." (References cited in DECOS, 2011).

The DECOS recommendation on 1,4-dioxane summarised the irritation/corrosion potential in experimental animals:

> **"Skin**
>
> "When applied undiluted under occlusive conditions for 1–15 minutes to rabbit skin 1,4-dioxane led to slight erythema and scale formation which was not completely reversible within 8 days (SCOEL BASF 1973; Zeller and Kühlern 1998a). In rats and mice the lowest irritating concentration was 80% (no further information available, SCOEL Sekizawa *et al*. 1994).
>
> **"Eyes**
>
> "Eye irritation (corneal opacity and conjunctival redness and slight to severe chemosis) was found after instillation of 0.05ml into rabbit eyes, which was not completely reversible within 8 days (SCOEL BASF 1973; SCOEL Zeller and Kühlern 1998b).
>
> **"Respiratory tract**
>
> "Irritating effects were noted in the respiratory tract of rats, mice, and guinea pigs in studies with insufficient documentation at concentrations presumably higher than 1,000ppm (3,600mg/m^3) (European Commission 2002)." (References cited in DECOS, 2011).

The **ECB** review of 1,4-dioxane summarised the sensitisation potential in experimental animals:

> "In a well-performed maximisation test, according to Guideline 84/449/EEC, 1,4-dioxane did not show skin sensitising properties. After a pre-test, in which undiluted 1,4-dioxane did not cause skin irritation, B6 female Pirbright White guinea pigs were induced with 5% (injection) and 100% (epidermal) test substance in the main test. Upon intradermal induction well-defined signs of erythema and oedema were observed. Upon percutaneous induction incrustation, well-defined erythema and slight oedema were noted, but these were caused by the intradermal induction. After the challenge with the undiluted substance no sensitisation reactions were observed (BASF, 1993)." (Reference cited in ECB, 2002).

The **ECHA CLP** proposal for 1,4-dioxane summarised the repeated dose toxicity in experimental animals:

> "Two subchronic repeated dose studies are available from Kasai *et al*. (2008) (inhalation route in F344 rats, **OECD TG** 413) and Kano *et al*. (2008) (oral administration in BDF 1 mice and F344 rats, OECD TG 408), that served as dose range finder studies for their long term carcinogenicity studies. Both studies found nuclear enlargement in several epithelial tissues along the respiratory tract (olfactory, respiratory, tracheal and bronchial). However, there is a clear difference in the location of the 1,4-dioxane induced enlarged nuclei of the nasal epithelial cells between the exposure routes (inhalation or oral administration) (Kasai *et al*. 2008). The respiratory epithelial area having the enlarged nuclei was expanded from the anterior portion to the entire region with inhaled 1,4 dioxane. On the other hand, the oral administration of 1,4-dioxane-formulated drinking water uniformly produced the nuclear enlargement over the entire region of the respiratory epithelium without any anterior–posterior gradient along the nasal passage. This difference in the route of exposure can be accounted for in terms of a first-pass effect such that the inhaled 1,4-dioxane comes into first contact with the anterior portion

of the respiratory epithelium, while the orally administered 1,4-dioxane is conveyed to the respiratory epithelial cells through the nasal blood flow after its first entrance in the gastrointestinal system including the liver (Kasai *et al*. 2008). In line with this, centrilobular swelling of hepatocytes was observed at lower estimated body doses to 1,4 dioxane via the oral route (≥126mg/kg bw/day) in comparison to exposure via inhalation (3200ppm corresponding to an estimated 2336mg/kg bw/day).

"Other histopathological findings in the liver include single cell necrosis and **GST-P** positive liver foci at predominantly high doses. The summarized histopathological findings in the liver and nasal cavity, are in line with the observed carcinomas found in the longer term (2-year) studies reported by Kano *et al*. (2009) and Kasai *et al*. (2009)." (References cited in ECHA, 2018).

The DECOS recommendation on 1,4-dioxane summarised the reproductive/ developmental toxicity in experimental animals:

"Fertility

"Decreased mineralisation in the testis of Crj:BDF1 mice was observed in a carcinogenicity study at a dose of 250mg/kg bw/d (SCOEL: Yamazaki *et al* 1994; SCOEL: Japan Bioassay Research Center 1998). In further oral 13-week studies and in the oral and inhalatory chronic toxicity/carcinogenicity studies no histopathological effects were observed in the reproductive organs of mice and rats.

"Developmental toxicity

"Groups of 17–20 pregnant Sprague-Dawley rats received by gavage 0, 0.25, 0.5 and 1.0ml 1,4-dioxane/kg bw in water during days 6–15 of gestation. The animals were killed on day 21 of pregnancy (SCOEL: Giavini *et al*. 1985). The females treated with 1ml/kg bw showed a slightly smaller weight gain during treatment, which continued into the second stage of gestation. This could be due to reduced consumption of food, which was especially evident in the first 2 days of treatment. However, a toxic effect of the solvent could not be excluded. Number of implantations and live fetuses did not differ compared to controls. The frequency of major malformations remained within normal limits for all groups, and no deviations were found regarding minor anomalies and variants when compared with the control group. At the highest dose level a significant retardation was found in the area of the sternum. There was no indication of teratogenicity. The authors stated that the fetal retardation could be ascribed to maternal toxicity. The **NOAEL** for maternal and embryotoxicity in this study was 0.5ml/kg bw, equivalent to 517mg/kg bw." (References cited in DECOS, 2011).

The DECOS recommendation on 1,4-dioxane summarised the genotoxic potential in experimental animals and *in vitro* test systems:

"As no genotoxicity studies of 1,4-dioxane in germ cells were found, the Committee is not able to make a conclusion whether 1,4-dioxane is mutagenic in germ cells."

"1,4-Dioxane was investigated in genotoxicity tests for the 3 endpoints of genotoxicity: gene mutations, structural and numerical chromosome aberrations. The Committee noted that in the majority of the animal studies no data on cytotoxicity were reported, which makes it difficult to interpret the outcomes. Also in most studies dose levels were used exceeding the limit

dose, making them less relevant to determine the genotoxicity of 1,4-dioxane. Furthermore, the differences in outcomes among the studies could also be partially explained by the use of a small number of animals, different dose regimen and testing methods.

"1,4 Dioxane did not induce gene mutations in bacteria nor in mammalian cells *in vitro*. Exposure to 1,4-dioxane did not result in an increase in cells with chromosome aberrations or micronuclei. The majority of the supporting genotoxicity tests (Table 3) confirmed the negative findings in *in vitro* tests.

"Unexpectedly, the *in vivo* genotoxicity studies gave contradictory results. Exposure to high doses of 1,4-dioxane, above the limit dose of 2,000mg/kg bw, resulted in an increase of cells with micronuclei indicating to a cytotoxic rather than a genotoxic effect. Occasionally positive results were also found in micronucleus tests with doses below the limit dose of 2,000mg/kg bw. The Committee cannot ignore these positive findings and considers that 1,4-dioxane also has a genotoxic potential. Aneuploidy was not observed. The majority of the supportive *in vivo* genotoxicity tests (Table 4) confirmed the *in vivo* results.

"As the important *in vitro* tests are negative but part of the *in vivo* tests unexpectedly positive predominantly at doses above the limit dose, it can be concluded that 1,4-dioxane has to be considered as a non-stochastic genotoxic substance and that the positive results may be due to cytotoxicity and thus proliferation induction. The positive results found in the tests measuring replicative **DNA** synthesis as a marker for cell proliferation confirm this mode of action. Since occasionally positive results in the micronucleus tests were found at doses below the limit dose of 2,000mg/kg bw a stochastic genotoxic mechanism as secondary mode of action cannot be excluded." (DECOS, 2015).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] evaluation of 1,4-dioxane concluded that:

There is *inadequate evidence* in humans for the carcinogenicity of 1,4-dioxane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,4-dioxane.

With an overall evaluation that:

1,4-Dioxane is *possibly carcinogenic to humans (Group 2B)* (IARC, 1999).

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

"1,4-Dioxane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals." (NTP RoC, 2016).

The New Zealand EPA classifies 1,4-dioxane as 6.7A – a substance known or presumed to be a human carcinogen (EPA, 2019).

Humans

The DECOS recommendation on 1,4-dioxane summarised the carcinogenicity data in exposed humans:

> "The Committee noted the low quality of study reporting, in that data were obtained from secondary sources, and that study details were missing. Also, the size of the cohorts, and thus the power of the studies, were low. In none of the studies evidence for carcinogenicity due to occupational exposure to 1,4-dioxane could be assessed." (DECOS, 2015).

Animals

The DECOS recommendation on 1,4-dioxane summarised the carcinogenicity data in experimental animals:

> "Male F344/DuCrj rats (50/group) were whole-body exposed to 0, 180, 900 and 4,500mg 1,4-dioxane/m^3 [0, 50, 252 and 1,260ppm], for 6 hours a day, 5 days/week for 104 weeks (Kasai *et al*., 2009). Details on tumour incidences are shown in Table 7. In summary, 1,4-dioxane induced a statistically significant increase in hepatocellular adenomas (highest exposure group only), peritoneal mesothelioma (two highest exposure groups), and in nasal squamous cell carcinoma (highest exposure group only). The investigators also reported on pre-neoplastic lesions, such as squamous cell metaplasia, characterized by replacement of transitional and respiratory epithelia by squamous epithelium with or without keratinisation occurred in rats exposed to 900mg/m^3 [252ppm] and higher. In addition, increased incidences of nuclear enlargement in the respiratory and olfactory epithelia, and atrophy and respiratory metaplasia in the olfactory epithelium, were noted in the nasal cavity of male rats exposed at 180mg 1,4-dioxane/m^3 [50ppm] and higher. Torkelson exposed Wistar rats to 400mg 1,4-dioxane/m^3 [112ppm] for 7 hours a day, five days a week for a total of 2 years. The substance did not induce neoplastic lesions." (References cited in DECOS, 2015).
>
> "A number of animal carcinogenicity studies have been performed in which animals received 1,4-dioxane orally in drinking water (see Table 6). Regarding the well-performed studies, all showed that 1,4-dioxane induced tumours in for instance the nasal cavity and the liver of rats and mice. Details on tumour incidences for the distinctive studies are shown in the Tables 8 to 12. In addition, the tumour development was preceded by the induction of non-neoplastic lesions, which progressed to hepatocellular adenoma and carcinoma in rats and mice and to nasal squamous cell carcinoma in rats at higher dosages. Liver tumours were observed at higher tumour incidences in rats and mice from a concentration of approximately 0.05% 1,4-dioxane and higher, whereas neoplastic lesions in the nose were observed in rats at a concentration of 0.5% 1,4-dioxane and higher." (References cited in DECOS, 2015).
>
> "The Committee noted the low quality of the animal carcinogenicity studies on dermal exposure and administration of 1,4-dioxane by intraperitoneal injection. For this reason, the Committee considers these studies not relevant in assessing the carcinogenic properties of the substance." (DECOS, 2015).

The ECHA CLP proposal for 1,4-dioxane noted that:

> "In summary, three tumour types have been observed in the literature: peritoneal mesothelioma, hepatocellular adenoma/carcinoma and squamous cell carcinoma. Significant effects have been observed for all three endpoints

in the highest dose groups. Peritoneal mesothelioma's are already observed to a significant extent in the mid-dose group of rats (exposure by inhalation, 250ppm). When exposed to 1,4 dioxane via the drinking water, the incidence of hepatocellular adenoma's and carcinoma's is higher compared to peritoneal mesothelioma's in contrast to exposure via inhalation. The incidence of squamous cell carcinoma's in the nasal cavity seems similar for both exposure routes. Additionally, the incidence of liver tumours is statistically increased in the mid-dose group of the study with mice (orally exposed) by Kano *et al*. 2009. However no peritoneal mesothelioma's were reported." (References cited in ECHA, 2018).

"To help determine the carcinogenic potency of 1,4 dioxane and set substance specific exposure limits, **T25** values according to EC (1999) were determined. The most sensitive endpoint in the studies by Kano *et al*. (2009) and Kasai *et al*. (2009) were used as these are the key studies available.

Kasai *et al* (2009).
Species and exposure route: Rats, inhalation.
Endpoint: Peritoneal mesothelioma in 14/50 (28%) rats at 250ppm by inhalation (second highest dose is closer to T25 than the incidence in the high dose group), and 2/50 (4%) at 0mg/kg bw/day
Net incidence: 14x((100/50)-2x(100/50))/(100-2x(100/50)) = 25%
Daily dose: 250.9ppm, at a rate of 6 l/h 6h/day with a weight of 500g (males only). *The air concentration in mg/m³ is 250.9ppm x 0.0409 x 88.12 g/mol = 904.27mg/m³*. Therefore the exposure is 904.27/1000 x 6l/h x 6h/day = 32.6mg/day equal to 65.2mg/kg bw/day in the male rats assuming 100% uptake.
Exposure frequency: 5/7 days per weeks
Exposure duration: 104 weeks is considered the general life span of the rats, therefore no correction is necessary.
T25: 65.2mg/kg bw/day x 25/25x 5/7 x 104/104 = 46.6mg/kg bw/day." (References cited in ECHA, 2018)

4.3 Absorption, distribution, metabolism and excretion

The DECOS recommendation on 1,4-dioxane summarised the **ADME**:

Absorption

"Four healthy volunteers inhaled 50ppm 1,4-dioxane (180mg/m³) for 6 hours, after which the blood and the urine was examined (Young *et al*., 1977). The substance was rapidly and extensively absorbed as evidenced by a rapid accumulation in plasma. Limited human data are available to evaluate the oral or inhalatory absorption of 1,4-dioxane.

"1,4-Dioxane was rapidly and almost completely absorbed after oral and inhalation exposure of mice (Sweeney *et al*., 2008)."

"Dermal absorption occurs, but it is low, probably due to evaporation of the material. In experiments with Rhesus monkeys, 2.3 and 3.4% of the dioxane, which was applied non occlusively as a methanol solution or as lotion on the forearm skin, was excreted in the urine (Marzulli *et al*., 1981). *In vitro* studies show that 12% of an applied dose passes through excised skin under occlusion, and only 0.3% when not occluded (ECETOC 1983)."

Distribution

"No data are available for the distribution of 1,4-dioxane in human tissues. In addition, no data are available for the distribution of 1,4-dioxane in animals following oral or inhalation exposure. After intraperitoneal administration of

^{3}H-labelled dioxane to rats, ^{3}H label was found in all tissues investigated at comparable levels (Woo *et al*., 1977) between 1 and 16 hours after administration. Mikheleev *et al*., (1990) report similar findings."

Elimination and pharmacokinetics

"In humans exposed for 6 hours to 180mg 1,4-dioxane/m^{3} [50ppm] (in a chamber under dynamic airflow conditions) dioxane in plasma rapidly accumulated to nearly steady state after 4 hours of exposure. It was excreted in urine as its metabolite ß-hydroxyethoxyacetic acid (**HEAA**) over the next 24 hours of which approx. 50% during the first 6 hour period. In humans exposed for 6 hours to 180mg 1,4-dioxane/m^{3} (50ppm) 99.3% of the absorbed dose (assuming that urinary excretion was the only excretory route) was eliminated via the urine as ß-hydroxyethoxyacetic acid (HEAA); the remainder was unchanged dioxane (Young *et al*., 1977). After the 6hr exposure period the plasma 1,4-dioxane concentration decreased exponentially, indicating that the elimination was not saturated. The plasma elimination T½ was 59 minutes (Young *et al*., 1977).

"Physiologically-based pharmacokinetic (**PB-PK**) models were developed by Reitz *et al*., (1990) and Leung and Paustenbach (1980), which were further improved by Sweeney *et al*., (2008). The plasma concentrations as well as HEAA urinary excretion after exposure to dioxane by inhalation or gavage in mice and rats could reasonably well be predicted, but the human volunteer data of Young *et al*., (1977) did not fit adequately in the model. Only the urinary excretion data of Young *et al*., (1978) were well predicted by the model. A physiologically based pharmacokinetic modelling study indicates that 1,4-dioxane may also be excreted into human milk (Fisher *et al*., 1997).

"1,4 -Dioxane is rapidly excreted in rats via the urine. The major metabolite is 2-hydroxyethoxyacetic acid (HEAA) (Woo *et al*., 1977a,b). At low pH, HEAA is rearranged (reversibly) to 1,4-dioxan-2-one."

Metabolism

"1,4-Dioxane is metabolized by cytochrome P-450's, possibly of the 2A and 2D family (Sweeney *et al*., 2008). Induction of the cytochrome P-450 enzymes increases the rate of HEAA formation, whereas inhibition decreases HEAA formation (Woo 1977b, Woo 1978).

"Repeated oral administration of 1,000mg/kg of 1,4-dioxane induced dioxane metabolism in rats, but at doses of 10mg/kg no such effect was observed (Young *et al*., 1978).

"At a single oral dose of 20mg/kg in mice the metabolism was so rapid that 1,4-dioxane could hardly be detected in blood; saturation of metabolism seemed to occur above 200mg/kg (Sweeney *et al*., 2008).

"In rats the capacity to metabolise 1,4-dioxane to HEAA is also limited. A single oral dose of 10mg/kg bw was rapidly metabolised and excreted (as HEAA) via the urine, while a single oral dose of 100 1,000mg/kg bw, saturated the metabolism, resulting in a decreased proportion of urinary excretion of HEAA, and increased excretion of 1,4-dioxane in urine and the expired air (Dietz *et al*., 1982, Reitz *et al*., 1990, Young *et al*., 1978). Young *et al*., (1978) observed a statistically significant increase of $^{14}CO_2$ excretion at multiple oral doses of ^{14}C-labelled dioxane compared to the control; it is unclear as yet how this mechanistically reflects metabolism of dioxane." (References cited in DECOS, 2015).

The DECOS recommendation on 1,4-dioxane summarised the mechanistic data for carcinogenesis:

> "The mechanism for carcinogenicity appears to be primarily non-genotoxic, involving the saturation of one metabolic pathway and the increasing prominence of an alternative one which produces the reactive, cytotoxic metabolite 2-hydroxyethoxyacetaldehyde (SCOEL 2004). 1,4-Dioxane-induced nasal tumours are considered to result primarily from the injury of cells in the respiratory and olfactory epithelia and subsequent regenerative cell proliferation, as evidenced by squamous cell metaplasia and hyperplasia which can be regarded as a pre-neoplastic lesion (Kasai *et al*. 2009). An increased incidence of hepatocellular tumours was only seen at high exposure levels and together with hepatocellular injury, evidenced by the necrosis of hepatocytes and enhanced cytolytic release of liver enzymes such as **AST**, **ALT**, **ALP**, and **gamma-GT** into plasma. The European Commission (2002) and SCOEL (2004) concluded that 1,4-dioxane-induced carcinogenesis is primarily driven by a cytotoxic/proliferative, non-genotoxic mode of action. However, at elevated dose levels genotoxic activity is also apparent, based upon repeated positive findings in micronucleus assays in liver and bone marrow of several strains of mice (SCOEL: Mirkova 1994; SCOEL: Tinwell *et al*. 1994; SCOEL: Morita and Hayashi 1998; Roy *et al*. 2005). Roy *et al*. (2005) demonstrated that the increased frequency of micronuclei is primarily due to chromosome breakage." (References cited in DECOS, 2011).

Douron *et al*. (2017) reanalysis of relevant data on 1,4-dioxane carcinogenesis and mutagenesis concluded that:

> "In the current work, a reanalysis of data from two chronic mouse cancer bioassays on 1,4-dioxane, one 13-week mouse study, seven rat cancer bioassays, coupled with other data such as 1,4-dioxane's negative mutagenicity, its lack of up-regulated DNA repair, and the appearance of liver tumors with a high background incidence, support the conclusion that rodent liver tumors, including those in mice, are evoked by a regenerative hyperplasia **MOA**. The initiating event for this MOA is metabolic saturation of 1,4-dioxane. Above metabolic saturation, higher doses of the parent compound cause an ever increasing toxicity in the rodent liver as evidenced by higher blood levels of enzymes indicative of liver cell damage and associated histopathology that occurs in a dose and time related manner. Importantly, alternative modes of action can be excluded. The observed liver toxicity has a threshold in the dose scale at or below levels that saturate metabolism, and generally in the range of 9.6–42mg/kg-day for rats and 57 to 66mg/kg-day for mice. It follows that threshold approaches to the assessment of this chemical's toxicity are supported by the non-mutagenic, metabolic saturation kinetics, and cytotoxicity-generated regenerative repair information available for 1,4-dioxane promoted rodent liver tumors." (Douron *et al*., 2017).

In contrast, Gi *et al*. (2018) reported a study in ***gpt*** delta transgenic F344 rats that concluded 1,4-dioxane was a genotoxic hepatocarcinogen and induced hepatocarcinogenesis through a mutagenic mechanism of action [MOA]:

> "To determine the *in vivo* mutagenicity of 1,4-dioxane, gpt delta transgenic F344 rats were administered 1,4-dioxane at various doses in the drinking water for 16 weeks. The overall mutation frequency (MF) and **A:T**- to -**G:C** transitions and A:T- to -T:A transversions in the gpt transgene were significantly increased by administration of 5000ppm 1,4-dioxane. A:T- to -T:A transversions were

> also significantly increased by administration of 1000ppm 1,4-dioxane. Furthermore, the DNA repair enzymem**gMT** was significantly induced at 5000ppm 1,4-dioxane, implying that extensive genetic damage exceeded the repair capacity of the cells in the liver and consequently led to liver carcinogenesis. No evidence supporting other MOAs, including induction of oxidative stress, cytotoxicity, or nuclear receptor activation, that could contribute to the carcinogenic effects of 1,4-dioxane were found." (Gi et al., 2018).

While Itoh and Hattori (2019) reported a series of liver and bone marrow tests and a ***Pig-a*** assay in rats that concluded 1,4-dioxane was clastogenic in the liver [at ≥1,000mg/kg b.w. p.o., depending on test system] but not genotoxic in the bone marrow of rats:

> "For the liver micronucleus test, we performed the juvenile animal method and two methods using partial hepatectomy (**PH**), dosing before PH or dosing after PH. We also evaluated the *in vivo* mutagenicity of 1,4-dioxane by *Pig-a* gene mutation assay using rat peripheral blood. As a result, all methods of liver micronucleus test showed an increase in the frequency of micronucleated hepatocytes by 1,4-dioxane. The dosing before PH, a suitable method for detecting structural chromosome aberration inducers, showed the clearest response for micronucleated hepatocytes induction among the three methods. This finding is consistent with a previous report that 1,4-dioxane induces mainly chromosome breakage in the liver. Negative results were obtained in the bone marrow micronucleus test and *Pig-a* gene mutation assay in our study." (Itoh and Hattori, 2019).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

5.2 DECOS

5.3 SCOEL

5.4 ACGIH®

5.5 Safe Work Australia

5.1 Other exposure standards

Table 3 below shows 1,4-dioxane exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia	10	36		
Austria	20	73	40	146
Belgium[1]	20	73		
Canada – Ontario	20			
Canada – Québec	20	72		
Denmark	10	36	20	72
European Union	20[2]	73		
Finland	10	36	40[3]	150[3]
France	20[4]	73[4]		
Germany – **AGS**	20	73	40[3]	146[3]
Germany – **DFG**	10	37	20[3]	74[3]
Hungary		10		
Ireland	20	73		
Italy[5]	20	73		
Japan – **MHLW**	10			
Japan – **JSOH**	1	3.6		
Latvia	5.5	20		
New Zealand	25	90		
People's Republic of China		70		
Poland		50		
Romania	20	73		
Singapore	25	90		
South Korea	20	72		
Spain[5]	20	74		
Sweden	10	35	25[3]	90[3]
Switzerland	20	72	40	144
The Netherlands		20		
Turkey	20	73		
USA – **NIOSH**			1[6]	3.6[6]
USA – **OSHA**	100	360		
UK	25	91	100	366

TABLE 3: Exposure standards for 1,4-dioxane 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] 15 minutes average value.

[4] Restrictive statutory limit values.

[5] skin.

[6] **Ceiling limit values**.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on 1,4-dioxane were DECOS, SCOEL, ACGIH® and Safe Work Australia.

5.2 DECOS

The Dutch Expert Committee on Occupational Standards [DECOS] recommended an **HBROEL** TWA 8 hours for 1,4-dioxane of 20mg/m³ (6ppm) (DECOS, 2011).

The rationale for their conclusions was:

> "DECOS considers the nasal lesions (increased incidence of nuclear enlargement in the respiratory and olfactory epithelia) found in rats after lifetime exposure to 1,4-dioxane as the critical effect. In addition, the Committee is of the opinion that these nasal lesions in the epithelium are precursor events in the development of nasal tumors. The nasal lesions are found at lower levels of exposure than the levels causing nasal tumors. Therefore, the Committee assumes that preventing increased nuclear enlargement in the respiratory and olfactory epithelia, will prevent the development of nasal tumours as well.
>
> "In deriving a health based recommended occupational exposure limit (HBROEL), the Committee preformed bench mark dose analyses on the critical effects. However, a **BMD** analysis of the relevant data revealed the BMD approach not to be applicable. Therefore, the Committee takes the LOAEL of 180mg/m³ (50ppm) found in the chronic inhalation study of Kasai *et al*. (2009) as a starting point. For the establishment of the HBROEL, uncertainty factors are applied to compensate for the extrapolation from a LOAEL to a **NAEL**, for differences between rats and humans, for the duration of exposure, and for interindividual differences. For the extrapolation of the LOAEL to a NAEL, a factor of 3 is applied. An uncertainty factor to compensate for the differences between rats and humans is unnecessary, as the critical effect is a local (non systemic) effect and nasal flux in rats is higher than in humans leading to higher exposure of nasal respiratory and olfactory epithelia. A factor compensating for the difference in duration of exposure (6 hours per day in the Kasai *et al*. study versus an 8-hour working day), is not deemed necessary as the rat is more sensitive to the observed effects than man. Finally, a uncertainty factor of 3 is used to compensate for the inter-individual differences.
>
> "Considering all these aspects, starting from a LOAEL of 180mg/m³ (50ppm) and using an extrapolation factor of 9, the Committee recommends an HBROEL TWA 8 hours for 1,4-dioxane of 20mg/m³ (6ppm). The Committee is of the opinion that this exposure limit will protect against the development of liver tumours as well." (DECOS, 2011).

DECOS also noted that:

> "The absorption rate of 1,4-dioxane through human skin *in vitro* is approximately 0.36µg/cm/h (ATSDR, 2006). When both hands and underarms (surface area 2000cm²) are exposed during eight hours the quantity absorbed would amount to (0.36x2000x8) 6mg. Via the inhalatory route an amount of 200mg is absorbed during 8 h exposure (10m³) to the recommended exposure limit of 20mg/m³, assuming 100% absorption. Therefore, skin absorption of 1,4-dioxane does not add considerably to the body burden. Therefore, a skin notation is not considered necessary by the Committee." (DECOS, 2011).

5.3 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] review of 1,4-dioxane concluded that:

> "On the basis of the Torkelson *et al* (1974) study reporting no effects in rats with lifetime exposure to 400mg/m^3 (111ppm) and the need to avoid eye irritation (seen in human volunteers at 50ppm; 180mg/m^3) a TWA of 20ppm (73mg/m^3) is proposed. There is no evidence for a proposal of a **STEL**."

The rationale for their conclusions was:

> "Torkelson *et al*.(1974) found in a 2 yr inhalation study in rats at an exposure level of 400mg/m^3 (111ppm) no evidence of toxicity, including carcinogenicity. 1,4 – dioxane has been shown to be carcinogenic in several drinking water studies in rats, mice and guinea pigs. The target organs were mainly the liver and nasal cavities. The mechanism appears to be non-genotoxic, involving the saturation of one metabolic pathway and the increasing prominence of an alternative one which produces the reactive, cytotoxic metabolite 2-hydroxyethoxyacetaldehyde. Studies in human volunteers exposed to 50ppm (180mg/m^3) 1,4-dioxane indicated almost total excretion of the inhaled dose as HEAA, with no indication of saturation of metabolism (Young *et al*, 1977). Human epidemiological studies did not show evidence of liver or kidney damage, nor clinical effects related to exposure of 1,4- dioxane, although the number of investigated people and the exposure was low (Thiess *et al*., 1976; Buffler *et al*. 1978). The overall death rate and the cancer death rate were not significantly increased compared to controls. The average exposures to 1,4 –dioxane were 54mg/m^3 and 90mg/m^3 respectively.
>
> "Irritation of the eye in volunteers was seen at a concentration of 180mg/m^3 (50ppm) in experimental settings (Young *et al*., 1977)." (SCOEL, 2004).

5.4 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review recommended a TLV-TWA of 20ppm [72mg/m^3] for occupational exposure to 1,4-dioxane to minimise the potential for liver and kidney toxicity and at higher concentrations, eye and respiratory tract irritation.

The rationale for their conclusions was:

> "Derivation of the **TLV** for 1,4-dioxane rests, in part, on interpretation of the rodent carcinogenicity data (Argus *et al*., 1965; Argus *et al*., 1973; Hoch-Ligeti *et al*., 1970; Hoch-Ligeti and Argus, 1970; Kociba *et al*., 1974; US NIC, 1978), taken together with data on genotoxicity (Stott *et al*., 1981; Zimmerman *et al*., 1985; Goldsworthy *et al*., 1991) and the pharmacokinetic profile of the compound in animals and humans (Braun, 1977; Woo *et al*., 1977a; Kociba *et al*., 1975; Young *et al*., 1978; Woo *et al*., 1977b; Young *et al*., 1977). There are no data to support a suggestion that dioxane-induced tumors arise from any mechanism other than an epigenetic (non-genotoxic) mode of action. In rodents, there is limited ability to metabolize 1,4-dioxane to β-hydroxyethoxyacetic acid, the major urinary metabolite in both rodents and humans. In addition, doses used in rodent drinking water carcinogenicity bioassays, where increased tumors were seen, were always greater than levels where saturation of metabolic clearance occurred. Inhalation exposure of both rats and humans at 50ppm dioxane showed no evidence of saturated dioxane clearance (Torkelson *et al*., 1974; Young *et al*., 1977). When dioxane exposures are so high that circulating

> concentrations accumulate, overt intoxication ensues, which precipitates systemic injury and subsequent carcinogenesis. No toxicity has been observed in either animals or humans where exposures were such that 1,4-dioxane could be eliminated by normal first-order processes; the corresponding no-observed-adverse-effect levels are 111ppm, 7 hours/day, 5 days/week for 2 years in rats (Torkelson *et al*., 1974) and at least 50ppm in workplace air for humans (Young *et al*., 1977)."
>
> "ACGIH believes that the TLV should be derived from the data on hepatotoxic and nephrotoxic effects which have occurred in workers and have been shown to result in animals from exposures one-tenth those required to produce a significant carcinogenic response." (References cited in ACGIH®, 2001).

ACGIH® also noted that:

> "The rapid absorption of dioxane following application to the skin of rabbits and guinea pigs led to signs of incoordination and narcosis, which, together with the systemic toxicity seen in workers following dermal exposure, warrants a **Skin** notation. Liver, lung, and nasal tumors in rats and mice fed dioxane in the diet or administered in drinking water are the basis for an A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, notification. Sufficient data were not available to recommend a **SEN** notation or a **TLV-STEL**." (ACGIH®, 2001).

5.5 Safe Work Australia

Safe Work Australia proposed an 8-h TWA of 5ppm to protect for irritation of the eye, effects in the upper respiratory tract and cancer in exposed workers.

In their review, they say, "Eye irritation is reported in human volunteers exposed at 50ppm. A **LOAEC** of 180mg/m^3 (50ppm) for nasal lesions is reported in a study in rats exposed by inhalation for two years (HCOTN, 2015). The TWA is derived from the LOAEC of 180mg/m^3 in rats with an application factor of 10 to account for no NOAEL and interspecies variation (same as HCOTN, 2015, except for rounding up). This is considered sufficient as the effect is local. A TWA of 18mg/m^3 [5ppm] is considered to protect for the local effects on eyes and respiratory tract and systemic effects for non-genotoxic carcinogenicity." (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne 1,4-dioxane

A common method to measure 1,4-dioxane exposure is using NIOSH Method 1602, Issue 2 (NIOSH, 1994).

Using this method an air sample of 0.5 to 15 litres is collected onto a sampling train consisting of a solid sorbent tube, with the sampling train set at 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.

This method can achieve a detection limit of 0.01mg per sample. This would allow quantitation of samples at an airborne concentration of 0.2ppm for a 15 litre air sample over 8 hours.

7.0
Discussion

WorkSafe's WES for 1,4-dioxane has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates 1,4-dioxane is locally and systemically toxic to humans, causing skin, eye and respiratory tract irritation and liver and kidney damage; and locally and systemically toxic to laboratory species causing skin, eye and respiratory tract irritation, liver and kidney damage, and nasal, peritoneal and liver tumours.

Based on the aforementioned documentation, informed by the conclusions of the DECOS, SCOEL, ACGIH® and Safe Work Australia reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 25ppm [90mg/m³] for inhalable fraction of 1,4-dioxane to be inadequate to manage health risks from possible workplace exposure:

- 1,4-Dioxane induced liver, nasal and peritoneal tumours in rodents (DECOS, 2015).
- 1,4-Dioxane was reported to give negative results in *in vitro* genotoxicity studies, but positive mutagenic results in *in vivo* micronucleus studies, particularly at doses above the limit dose of 2,000mg/kg b.w. (DECOS, 2015).
- The mechanism(s) by which 1,4-dioxane induces cancer appear to be predominantly non-stochastic genotoxic cytotoxicity and proliferation induction, possibly when doses that exceed the capacity of the primary metabolic pathway result in the increased formation of the cytotoxic metabolite, 2-hydroxyethoxyacetaldehyde (SCOEL, 2004).
- The DECOS, SCOEL, ACGIH® and Safe Work Australia reviews proposed **OEL**s for workplace exposures to 1,4-dioxane, based on threshold effects, although non-threshold effects cannot be excluded.
- The DECOS proposed an OEL for 1,4-dioxane, with a HBR-OEL at 6ppm [20mg/m³], based on non-neoplastic and pre-neoplastic changes in the nasal cavity of rats (nuclear enlargement of the olfactory and respiratory epithelium, and atrophy and metaplasia of the olfactory epithelium), a LOAEL at 50ppm [180mg/m³], the lowest concentration tested (DECOS, 2011).
- Safe Work Australia proposed the lowest OEL for 1,4-dioxane, with a WES at 5ppm, based on the DECOS proposal (except they rounded down, whereas DECOS rounded up).
- The SCOEL noted eye irritation in volunteers also at 50ppm [180mg/m³] (SCOEL, 2004).
- More recent information reported that 1,4-dioxane can induce clastogenicity and gene mutations in *in vivo* test systems, and that a genotoxic element to the carcinogenicity of 1,4-dioxane cannot be excluded (Gi *et al*., 2018; Itoh and Hattori, 2019).

- The proposed WES-TWA of 5ppm [20mg/m^3] for 1,4-dioxane is set to be protective against all non-carcinogenic and non-genotoxic endpoints as cytotoxicity appears to be the trigger for toxicity, but may not be fully protective against carcinogenic effects as the full implications of the potential genotoxicity of 1,4-dioxane are not fully understood.
- A *skin notation* is justified for 1,4-dioxane, based on the systemic toxicity reported in workers and experimental animals after dermal absorption (ACGIH®, 2001).
- Available information indicates that 1,4-dioxane is not a sensitiser, and a ***sen*** *notation* is not warranted.

8.0 Recommendations

WorkSafe considers its current WES-TWA of 25ppm [90mg/m^3] of 1,4-dioxane to be inadequate to protect workers exposed in the workplace, based on today's scientific understanding.

It is proposed that WorkSafe:

1. adopt a WES-TWA for 1,4-dioxane of 5ppm [18mg/m^3];
2. retain the skin notation for 1,4-dioxane.

Noting that the proposed WES-TWA of 5ppm [18mg/m^3] for 1,4-dioxane may not eliminate all risk, due to the possible genotoxic potential of 1,4-dioxane and the impact of dermal absorption, so exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

Appendix 2: HSNO health-related hazardous substance classifications

Appendix 3: References

Appendix 1: Glossary

TERM	MEANING
A	Adenosine, purine nucleoside [component of DNA, RNA etc.].
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
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.
ALP	Alkaline phosphatase.
ALT; ALAT	Alanine Aminotransferase – an enzyme.
AST; ASAT	Aspartate Aminotransferase.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BMD	Bench-Mark Dose.
C	Cytidine, nucleoside.
Ceiling or Ceiling Limit Value	Ceiling Limit Value – absolute exposure limit that should not be exceeded at any time.
CLP	Classification, Labelling and Packaging – EU regulation.
DECOS	Dutch Expert Committee on Occupational Standards. A committee of the *Health Council of the Netherlands*. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DNA	Deoxyribonucleic acid.
ECB	European Chemicals Bureau – an agency of the European Union and predecessor of the ECHA.
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
G	Guanosine, purine nucleoside.
gamma-GT/ γGT	Gamma-glutamyltranspeptidase.
gpt	Gene coding enzyme glutamic pyruvic transaminase, GPT [also known as alanine amino transferase, ALT].
GST-P	Glutathione *S*-Transferase [Placental type].
HBR-OEL	Health-based recommended occupational exposure limit. A European Union term.
HEAA	2-Hydroxyethoxyacetic acid or ß-hydroxyethoxyacetic acid.
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].

TERM	MEANING
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009). (*cf*. Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
IOELV	Indicative Occupational Exposure Limit Value (health-based, SCOEL parameter).
JSOH	Japan Society for Occupational Health.
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.
mg/kg b.w. or mg/kg bw	Milligram of substance per kilogram body weight.
mg/m3	Milligrams of substance per cubic metre of air.
MGMT	*O*^{6}-Alkylguanine DNA alkyltransferase or *O*^{6}-methylguanine DNA methyltransferase, DNA repair enzyme.
MHLW	Japanese Ministry of Health, Labour and Welfare.
MoA; MOA	Mode of Action; Mechanism of Action.
NICNAS	National Industrial Chemicals Notifications and Assessments Scheme – 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.
NAEL	No Adverse Effect Level.
NOAEL	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).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
PBPK	Physiologically based pharmacokinetic: a modelling technique for predicting the absorption, distribution, metabolism and excretion [ADME] of substances in humans and other animal species.
PH	Partial hepatectomy.
Pig-a	Gene encoding phosphatidylinositol N-acetylglucosaminyltransferase subunit A.
ppm	Parts of vapour or gas per million parts of air.
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.

TERM	MEANING
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.
STEL (WES-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.
T	Thymidine, deoxythymidine.
T25	The dose eliciting a 25% increase in the incidence of a specific tumour above the background level (that is, after correction for spontaneous incidence) within the standard lifespan of that species.
TG	Test Guidelines. 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 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.
US EPA	United States Environmental Protection Agency.
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-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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