Workplace Exposure Standard (WES) review

4,6-DINITRO-O-CRESOL
(CAS NO: 534-52-1)

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New Zealand Government

WORKSAFE
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appendices

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for 4,6-dinitro-*o*-cresol should be changed.

The WES review considers the potential for exposures to 4,6-dinitro-*o*-cresol in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures given currently available analytical methods.

The review includes a recommendation to change the WorkSafe WES for 4,6-dinitro-*o*-cresol, which is currently set at a **WES-TWA** of 0.2**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: DNOC; Dinitro-*o*-cresol; 3,5-Dinitro-2-hydroxytoluene; 2-Methyl-4,6-dinitrophenol; DNC; 3,5-Dinitro-*o*-cresol; 4,6-Dinitro-2-methyl phenol.

2.0 Chemical and physical properties

4,6-Dinitro-*o*-cresol is a yellow, crystalline, odourless solid at room temperature (**ACGIH**®, 2019; **ATSDR**, 2018).

Chemical and physical properties 4,6-dinitro-*o*-cresol include:

Molecular weight	198.13g/mol
Formula	$C_7H_6N_2O_5$
Specific gravity/density	1.58g/m^3 at 20°C
Melting point	87.5°C
Boiling point	312°C
Vapour pressure	1.05 x 10^{-4}mmHg at 25°C; 3.6 x 10^{-4}mmHg at 35°C
Vapour density	6.84 [air = 1]
Saturated vapour concentration	0.158ppm at 25°C
Explosive limits	30g/m^3 [dust]
pKa	4.46, 4.38, 4.35
Solubility	Slightly soluble in water [130mg/L at 15°C]; soluble in ethanol [4.3g/100g], acetone [100g/100g], benzene [37g/100g], chloroform [37%], glacial acetic acid [23.5%], petroleum ether [0.5%]
Conversion factors	1mg/m^3 = 0.12ppm 1ppm = 8.01mg/m^3

ACGIH®, 2019; **ATSDR**, 2018; **NLM** PubChem, 2019.

TABLE 1: Physicochemical properties of 4,6-dinitro-*o*-cresol

Health-related hazard classifications for 4,6-dinitro-*o*-cresol:

SUBSTANCE	**HSNO CLASSIFICATION**
CAS No.	534-52-1
Classification	6.1B (All); 6.1B (O); 6.1B (D); 6.1B (I); 6.3A; 6.5B; 6.6B 8.3A

TABLE 2: **HSNO** hazard classifications of 4,6-dinitro-*o*-cresol (**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

4,6-Dinitro-*o*-cresol is used as a chemical intermediate for synthesis of fungicides and biologically active compounds, dyes and pharmaceuticals; and, as a polymerisation inhibitor for vinyl aromatic compounds (ATSDR, 2018).

4,6-Dinitro-*o*-cresol has uses as a non-systemic stomach poison and contact insecticide, and contact herbicide, particularly against broad-leaved plants, but such uses have been cancelled in many jurisdictions including the EU, US and NZ (ATSDR, 2018; ACGIH®, 2019).

Historically 4,6-dinitro-*o*-cresol has been used as a weight-reduction drug (ATSDR, 2018).

Occupational exposure to 4,6-dinitro-*o*-cresol can occur during production, storage, transportation and end-use.

Workers can be exposed to 4,6-dinitro-*o*-cresol aerosols via inhalation and eye or dermal contact (**NIOSH**, 2015; US EPA, 2000).

The number of workers exposed or potentially exposed to 4,6-dinitro-*o*-cresol in New Zealand workplaces is unknown.

Statistics New Zealand 2018 data indicate that 3,880 New Zealand workers were working in the areas of:

- basic organic chemical manufacturing
- pesticide manufacturing
- pharmaceutical and medicinal product manufacturing (NZ.Stat, 2019).

It is not known if the substance is used as a herbicide or insecticide in New Zealand and if so how many workers may be exposed.

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The **SCOEL** recommendation for 4,6-dinitro-*o*-cresol summarised the acute toxicity potential in humans:

> "Information on acute toxicity in humans has been obtained from cases of high-level occupational exposure and from earlier therapeutic use as a slimming aid. **DNOC** causes uncoupling of oxidative phosphorylation, resulting in depletion of **ATP** and, ultimately, increased glycolysis and glycogenolysis, inhibition of lipogenesis and increased degradation of fatty acids (Gasiewicz, 1991). Early symptoms are elevation of the basal metabolic rate and a rise in body temperature accompanied by fatigue, excessive sweating, unusual thirst and loss of weight (Gosselin, 1984, de Bruin, 1976). Acute poisoning is rapid, with either death or almost complete recovery occurring within 24–48h (Hayes, 1963, Morgan, 1982).
>
> "The lethal dose in humans is reported to lie in the range of 350 to 3000mg DNOC (**DFG**, 1976). A single oral dose of 75mg (approximately 1mg/kg body weight) is reported to have produced no toxic effects in five volunteers (Harvey, 1952, ACGIH, 1986), but data from earlier use as a slimming aid indicate that effects on basal metabolic rate (BMR) are likely at this level (Gasiewicz, 1991). Although the exposure data by air are limited in number and validity in most cases, exposure to a level of 4.7mg/m^3 was reported to result in similar symptoms to those reported following ingestion (ACGIH, 1991). These symptoms were not observed when the air concentration was reduced to 2.5mg/m^3. Reports of occupational poisonings following dermal contact with DNOC indicate ready absorption of DNOC through the skin." (References cited in SCOEL, 2004).

The New Zealand EPA classifies 4,6-dinitro-*o*-cresol as a 6.1B substance – a substance that is acutely toxic.

The **NIOSH** Skin Notation Profile for 4,6-dinitro-*o*-cresol noted:

> "No epidemiological studies or occupational exposure studies were identified following dermal exposure to dinitro-o-cresol. However, Buchinksii [1974] reported a fatality following application of an ointment containing dinitro-o-cresol on a 4-year-old. After the ointment was applied, the child vomited, complained of headache, and his skin, sclera, and visible mucosa appeared yellow in color [Buchinksii 1974]. The child lost consciousness, had tachycardia and convulsions followed by death [Buchinksii 1974]. Steer [1951] also reported the death of a worker following exposure to dinitro-*o*-cresol while spraying dinitro-o-cresol for several days. The worker was reported to have his hair, eyebrows, and pubic hair coated with dinitro-o-cresol, and his skin was faintly yellows [sic] and the palms of his hands and soles of his feet were stained yellow. The worker was sweating heavily and had irregular and labored breathing, increased pulse up to 160 beats per minute, and an increased temperature up to 104.8°Farenheit (F) [Steer 1951]. Jastroch *et al*. [1978] followed workers from three agro-chemical centers, of which 40 employees were exposed to dinitro-*o*-cresol, and noted that risk of exposure to dinitro-*o*-cresol was greatest during the manual preparation of the solution and during application. Three workers at the agrochemical centers were exposed to concentrations of dinitro-*o*-cresol greater than 30µg/ml; of these, one worker experienced sweating, dyspnea, weakness, mental disorientation, yellow discoloration on the skin, and evidence of parenchymal liver disease was present 14 days after intoxication [Jastroch *et al*. 1978].

> The other two workers experienced increased sweating, loss of appetite, and yellow discoloration on their skin [Jastroch *et al*. 1978]. Bidstrup and Payne [1951] described 8 cases where workers were exposed to dinitro-*o*-cresol. In most of these cases, the workers suffered from increased sweating and body temperature. Although inhalation likely contributed to exposure, several of the workers described by Bidstrup and Payne [1951] had hair, eyebrows, and/or skin that was stained by dinitro-o-cresol. Pollard and Filbee [1951] and King and Harvey [1953] noted that heat (increased environmental temperature) might have a marked effect on the metabolism of dinitro-*o*-cresol." (Reference cited in NIOSH, 2015).

The NIOSH Skin Notation Profile for 4,6-dinitro-*o*-cresol summarised the irritation/corrosion potential in exposed humans:

> "Numerous human and animal studies were identified for dinitro-*o*-cresol that reported direct effects on the skin. Human case reports described the staining of the skin following contact with dinitro-o-cresol [Bidstrup and Payne 1951; Steer 1951]. Several dermal studies were identified in which repeated application of dinitro-*o*-cresol resulted in no skin irritation in human volunteers. For example, no signs of dermal irritation were observed when the hands of two workers were exposed to a 20% solution of dinitro-*o*-cresol in oil for a period of two weeks to 17 days [Stott 1956] or when 0.5% or 1% dinitro-*o*-cresol solutions were applied to the backs of workers for patch testing [Lisi *et al*. 1987]. Repeated application of 2% dinitro-*o*-cresol solution to the shaved arm pits and to the anterior cubital surface of each arm of human volunteers for 30 days produced no dermal irritation [Ambrose 1942]." (References cited in NIOSH, 2015).

The New Zealand EPA classifies 4,6-dinitro-*o*-cresol as a 6.3A and 8.3A substance – a substance that is irritating to the skin and corrosive to ocular tissue, respectively.

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the sensitisation potential in exposed humans:

> "There are no substantiated reports of irritancy or allergenicity in humans, either dermal or in the respiratory tract. Patch testing of a substantial patient population having suspected allergic or non-allergic dermatitis with either 0.5% (n = 200) or 1% (n = 492) DNOC did not result in any treatment-related skin reactions (Lisi *et al*., 1986, 1987)." (References cited in SCOEL, 2004).

The New Zealand EPA classifies 4,6-dinitro-*o*-cresol as a 6.5B substance – a substance that is a contact sensitiser.

The SCOEL Recommendation 4,6-dinitro-*o*-cresol summarised the repeated dose toxicity in humans:

> "There are a number of early reports of occupational intoxication following prolonged exposure to DNOC (for example, Malter, 1949; Steer, 1951, Bidstrup & Payne, 1951; Heyndrickx *et al*, 1962, 1964, Prost *et al*, 1973; Jastroch *et al*., 1978). Reports of occupational poisonings following dermal contact with DNOC indicate ready absorption of DNOC through the skin. Symptomology was similar to that reported following acute exposure, including weight loss, fatigue, excessive sweating and development of yellow coloration of the skin and conjunctiva. Toxicity is enhanced in hot environmental conditions,

reflecting DNOC's hyperthermia-inducing effects (Bidstrup & Payne, 1951) and fatalities have been reported following prolonged exposure (Malter, 1949; Bidstrup & Payne, 1951). Cases of occupational intoxication declined markedly as recognition of the toxicity of DNOC increased, and under the use conditions pertaining in European agriculture prior to the removal of DNOC from the EU market, there were few reports of overt toxicity (**WHO**, 2000).

"Levels in blood are considered to provide the most reliable indicator of the dose:response relationship for DNOC (DFG, 1998, WHO, 2000), in particular because of the ready absorption of DNOC through the skin. Although the data from the early occupational poisoning cases are limited for the purposes of deriving a dose:response relationship, clear clinical symptomology and even death were associated with blood levels above 70µg/ml (Steer, 1951, Jastroch *et al*., 1978). Harvey (1952) measured blood DNOC levels in volunteers given 75mg DNOC every day for either 5 (three subjects) or 7 days (two subjects). Blood levels were measured daily, 4 hours after dosing, and in two of the volunteers receiving DNOC for 5 days levels rose to approximately 20µg/ml, while in the third volunteer the level at the end of 5 days was approximately 40µg/ml. In the two volunteers receiving DNOC for 7 days, the blood DNOC level in one rose to approximately 38µg/ml, while in the other the level reached 48µg/ml. The latter showed signs of DNOC toxicity (headache, lassitude and malaise) (Harvey, 1952).

"Clinical biochemical changes indicative of liver and kidney damage have been reported in a number of the cases of occupational poisoning at elevated (>40 µg/ml) blood levels of DNOC (for example, Heyndrickx *et al*., 1962, 1964, Prost *et al*., 1973; Jastroch *et al*., 1978, Thiele *et al*., 1983). Jastroch and co-workers studied a group of 7 workers exposed to DNOC for periods ranging between 29 and 70 hours at a level of 2.5% in an agrochemical spray (Jastroch *et al*., 1978). Atmospheric levels of DNOC in this study averaged 0.103µg/m^3, well below the **MAK** value of 0.2µg/m^3 pertaining at that time. They reported clinical symptoms and biochemical changes in 3 of these workers, with associated blood levels of 36µg/ml, 36µg/ml and 69µg/ml respectively, while 2 workers with blood levels of 15µg/ml and 11µg/ml showed some elevation in aspartate aminotransferase (**AST**), which was already identified before spraying with DNOC. Clinical chemistry results were normal in the remaining 2 workers. More recently, Heuts (Heuts, 1993, cited in WHO, 2000) reported an absence of effect on liver function, as measured by several parameters, and no clinical symptomology in sprayers having <0.5µg/ml DNOC in blood. Although a threshold of 30–40µg/ml (30–40mg/l) for clinical symptomology of DNOC toxicity has been suggested (Jastroch *et al*., 1978, WHO, 2000), the small numbers involved in the Jastroch *et al* study and the low exposures involved in the Heuts study do not allow definite conclusions to be drawn about a possible Lowest-Observed-Adverse-Effect-Level (**LOAEL**) or a No-Observed-Adverse-Effect-Level (**NOAEL**) for DNOC in blood. However, it is generally assumed that a DNOC level of up to 10µg/ml (10mg/l) (DFG, 1998) or even 20µg/ml (20mg/l) (WHO, 2000) is unlikely to result in adverse health effects in humans." (References cited in SCOEL, 2004).

The US EPA review of 4,6-dinitro-*o*-cresol noted in their derivation of provisional subchronic and chronic oral **RfD** values:

"As noted earlier, the available human studies collectively suggest LOAELs in the range of 0.35 to 1.2mg/kg-day for humans ingesting DNOC for up to 1 year (see Table 3). The limitations across all of the human studies include deficiencies in reporting, lack of control groups, small numbers of exposed individuals, inconsistent dosing regimens, and brief exposure durations.

Subchronic and chronic animal studies support metabolic effects as the key endpoint for DNOC, most commonly manifested in these studies by changes in food consumption and body-weight gain (Ambrose, 1942; Spencer *et al*., 1948; Den Tonkelaar *et al*., 1983; Broadmeadow, 1991, as summarized in WHO, 2000), but also by more subtle indicators of metabolic disturbance (Den Tonkelaar *et al*., 1983). Effective doses in the animal studies are approximately an order of magnitude higher than in the human studies."

"Of these studies, Ibrahim *et al*. (1934) has been chosen as the principal study because on the whole, it was the best conducted and utilized an adequate number of human subjects (eight males and seven females). This study identifies DNOC-induced metabolic critical effects including reduced body weight, excessive perspiration and fatigue, and elevated BMR and body temperature, as well as ocular effects (that is, greenish-yellow coloration of the conjunctivae). Ibrahim *et al*. (1934) identifies a LOAEL of 0.8mg/kg-day for DNOC based on these effects, and this study is also supported by several other human studies (Dodds and Robertson, 1933; Plotz, 1936; Harvey *et al*., 1951) that identify analogous critical effects occurring in a similar dose range. Although the study by Mahlen (1938) utilized more subjects (56 cases), this study did not evaluate DNOC-induced metabolic effects, and a higher LOAEL of 1.2mg/kg-day was identified based on cataract development. Thus, the lower LOAEL of 0.8mg/kg-day for DNOC-induced metabolic and ocular effects distinguished in Ibrahim *et al*. (1934) is identified as the point of departure (**POD**)." (References cited in US EPA, 2010).

Animals

The SCOEL recommendation for 4,6-dinitro-*o*-cresol summarised the acute toxicity potential in experimental animals:

"In animals, reported **LD50** values for DNOC range from 20–85mg/kg bw orally in the rat, mouse and cat, 200–>2000mg/kg by the dermal route in the rat, rabbit, mouse and guinea pig and 40–230mg/m^3 by the inhalation route in rats or cats (as summarised in WHO, 2000). Signs of acute toxicity include hyperactivity, laboured respiration and convulsions, prior to death." (Reference cited SCOEL, 2004).

The NIOSH Skin Notation Profile for 4,6-dinitro-*o*-cresol summarised the irritation/ corrosion potential in experimental animals:

"In contrast, technical grade dinitro-*o*-cresol was shown to be a dermal irritant in animal studies. Spencer *et al*. [1948] observed slight irritation on the abdomen of rabbits after administration of 7 applications of a 3% alcohol solution of dinitro-*o*-cresol. However, no signs of dermal irritation were observed when a 2% aqueous solution of dinitro-*o*-cresol was applied daily to the depilated dorsal surface of rats and rabbits for 30 days [Ambrose 1942]. Twenty repeat applications of 4% dinitro-*o*-cresol solution in Dormant oil to the ears of rabbits produced slight irritation and a slight hyperplastic reaction and 5% dinitro-*o*-cresol solution in olive oil produced very slight simple irritation [Dow Chemical Company 1992]. The conflicting results on the irritation potential of dinitro-*o*-cresol may be explained by differences in applied concentration and vehicles among the studies. Predictions using the structure activity relationship model Deductive Estimation of Risk from Existing Knowledge (***DEREK***) for Windows indicate that the substance was negative for skin irritation." (References cited in NIOSH, 2014).

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the sensitisation potential in experimental animals:

> "Technical grade DNOC is however moderately irritating to rabbit skin (Driscoll, 1995a, cited in WHO, 2000) and is corrosive to the rabbit eye (Driscoll, 1995b, cited in WHO, 2000). It is also a skin sensitiser in the Guinea Pig Maximisation test (Driscoll, 1995c, cited in WHO, 2000)." (References cited in SCOEL, 2004).

The NIOSH Skin Notation Profile for 4,6-dinitro-*o*-cresol noted:

> "No predictive tests in animals (guinea pig maximization tests, Buehler tests, murine local lymph node as says or mouse ear swelling tests) were also identified. Based on structure activity relationship, *DEREK* for Windows predicted dinitro-*o*-cresol to be negative for sensitisation. Therefore, on the basis of the data for this assessment, dinitro-*o*-cresol is not assigned the **SK: SEN** notation." (References cited in NIOSH, 2014).

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the repeated dose toxicity in experimental animals:

> "A number of subacute, subchronic and chronic toxicity studies have been carried out in rats, mice, dogs and cats, via the oral or inhalation route (summarised in DFG, 1998, WHO, 2000). A dose level of 10mg/kg DNOC in the diet (equivalent to 2.5mg/kg bw/day) was considered to be a no effect level in a 90 day feeding study in the rat (den Tonkelaar *et al*, 1983), with some decrease in body weight, occasional deaths, increased blood urea nitrogen and decreases in **T3** and **T4** levels being seen at a dietary level of 100mg/kg (equivalent to 5mg/kg bw/day). In a 90 day study in dogs, the No Observed Adverse Effect Level (NOAEL) was considered to be 0.89mg/kg bw/day (Til, 1980, cited in WHO, 2000).
>
> "In a 104 week oral feeding study in rats at levels of 0, 2.5, 15 or 100ppm in the diet, equivalent to a daily intake of 0.12, 0.75 and 5.03mg/kg bw in females, and to 0.10, 0.59 and 4.12mg/kg bw in males, there were no clinical signs of toxicity and no effects on mortality or on body-weight (Broadmeadow, 1991, cited in WHO, 2000). Food consumption was slightly increased in high dose males compared with controls (+6%) from week 5 onwards. No significant changes were found in the haematological and biochemical parameters evaluated in the course of the study and there were no treatment-related histopathological changes). The **NOEL** was 0.59mg/kg bw/day (Broadmeadow, 1991).
>
> "Inhalation studies provide the most relevant animal studies for consideration of an occupational exposure limit for DNOC. Subchronic inhalation studies in cats showed death in 2/3 animals exposed to 2.0mg/m^3, 4h/day for 30 days, but only transient blood changes at 0.2mg/m^3, 4h/day for 60–90 days (Burkatskaya, 1965b). Popov *et al*. (1971) found no effects in rats exposed to 0.001mg/m^3 for an unspecified time throughout a 60 day period. No subacute, subchronic or chronic dermal exposure studies have been carried out in animals." (References cited in SCOEL, 2004).

The WHO **EHC** on dinitro-*ortho*-cresol noted:

> "Vos *et al*. (1983) tested DNOC in the category of compounds having no, or only marginal, effects on immunological parameters. Wistar-derived rats received DNOC in their diet at concentrations of 25, 100 and 400mg/kg of feed for 3 weeks. General toxicological effects were evaluated, in addition to the particular immunological parameters: lymphocyte and monocyte counts; serum **IgM** and **IgG** levels; weight and histopathology of thymus, spleen and lymph nodes. None of these parameters was significantly affected. DNOC was not considered as having the potential to induce disturbances in the immunological system." (Reference cited in WHO EHC, 2000).

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the reproductive/developmental toxicity in experimental animals:

> "In a 2-generation reproductive toxicity study in rats (Coles & Brooks, 1997, cited in WHO, 2000), maternal body weight, food consumption and group mean litter weight were reduced at the highest dietary dose level of 100mg/kg/day. The NOEL in this study was 30mg/kg/day in diet, equivalent to a highest systemic dose of 2.4mg/kg/ bw/day in **F1** males and 2.61mg/kg/ bw/day in F1 females. An oral developmental toxicity study in the rat at dose levels of 0, 5 and 25mg/kg/day showed a slightly increased resorption rate at the highest dose level of 25mg/kg/day. While this effect was not statistically significant, a NOAEL of 5mg/kg bw/day in the rat can be derived (Dickhaus & Heisler, 1984, cited in DFG, 1998). A parallel study in the mouse using similar dose levels showed no treatment-related effects (Dickhaus & Heisler, 1984). In the rabbit a NOAEL of 10mg/kg bw/day via either the oral or the dermal route was established, but higher oral dose levels resulted in external and/or visceral malformations, including microphthalmia and anopthalmia (Allen *et al*, 1990a, cited in WHO, 2000). Developmental toxicity was also evident via the dermal route, at dose levels of 30mg/kg bw/day and above (Allen *et al*, 1990b, cited in WHO, 2000)." (References cited in SCOEL, 2004).

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "The genotoxicity of DNOC has been investigated in a number of *in vitro* and *in vivo* genotoxicity assays, as summarized by WHO (2000). DNOC has been shown to have mutagenic potential in bacterial mutagenicity systems (strains TA98 and TA100) both in the presence and absence of metabolic activation (Sundvall *et al*, 1984). Sundvall showed that the mutagenic response obtained in the Ames test was markedly reduced or abolished when the nitroreductase strains TA98NR and TA100NR were used, indicating involvement of nitroreductase. Relevant to this was the demonstration by Ingebrigtsen and Froslie (1980) that DNOC was rapidly reduced to **6-ANOC** followed by further reduction to diamino-o-cresol (**DAOC**) in an *in vitro* study in the presence of rat caecal contents, indicating a metabolic role for intestinal flora. However, a more recent and better documented study (Hrelia *et al*, 1994) showed negative results in strains TA97, TA98, TA100 and TA102 with and without metabolic activation. The same study provided negative results in an **UDS** assay assessed by measuring **3H-TdR** uptake by **HPBL** grown in the presence of three doses of DNOC and 10mM hydroxyurea and in an *in vitro* SCE assay using HPBL cultured with three doses of the substance with and without metabolic activation. DNOC gave a positive result in the mouse lymphoma **HPRT** test (Martin, 1981, cited in WHO, 2000).

> "DNOC has been reported to induce chromosomal aberrations both *in vitro* in human lymphocytes and *in vivo* in mouse bone marrow (Nehez *et al*., 1978; 1981; 1984; Hrelia, 1994). Other *in vivo* chromosomal aberration studies have, however, yielded negative results in rat and mice (Marzin, 1991, cited in WHO, 2000; Kirkland, 1984, 1986 (cited in WHO, 2000)), and it can be concluded overall that DNOC is not a clastogen. DNOC has also been reported to produce a low but statistically significant increase in recessive lethal mutations and chromosomal aberrations in *Drosophila melanogaster* (Muller and Haberzettl, 1980), but was negative in the dominant lethal test in D.melanogaster (Waters and Auletta, 1981, cited in Hrelia,1994).
>
> "Overall, although it has been suggested that some of the genotoxic effects may be attributable to impurities in the technical product rather than to the pure substance, DNOC has been classified as a **category 3 mutagen** in the 25th Adaptation to Technical Progress of Directive 67/548/EEC ." (References cited in SCOEL, 2004).

The New Zealand EPA classifies 4,6-dinitro-*o*-cresol as a 6.6B substance – a substance that is a suspected human mutagen.

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] has no evaluation on the carcinogenic potential of 4,6-dinitro-*o*-cresol. (IARC, 2019).

The US National Toxicology Program [NTP] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of 4,6-dinitro-*o*-cresol (NTP RoC, 2019).

The New Zealand EPA does not classify 4,6-dinitro-*o*-cresol as 6.7A/B for carcinogenic potential (EPA, 2019).

Humans

No data were available from studies in humans on the carcinogenicity of 4,6-dinitro-*o*-cresol.

Animals

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the carcinogenicity data in experimental animals:

> "A 104 week oral feeding study in rats at levels of 0, 2.5, 15 or 100ppm in the diet, equivalent to a daily intake of 0.12, 0.75 and 5.03mg/kg bw in females, and to 0.10, 0.59 and 4.12mg/kg bw in males, showed no evidence of carcinogenicity (Broadmeadow, 1991, cited in WHO, 2000)." (SCOEL, 2004).

The WHO EHC on dinitro-*ortho*-cresol noted from the Broadmeadow (1991) study:

> "A NOEL of 0.59mg/kg b.w. per day was determined in males on the basis of increased food consumption, and 5.03mg/kg b.w. per day in females (highest administered dose)." (WHO EHC, 2000).

4.3 Absorption, distribution, metabolism and excretion

The SCOEL Recommendation for 4,6-dinitro-*o*-cresol summarised the **ADME**:

> "DNOC is rapidly absorbed following inhalation, ingestion and via skin contact (Burkatskaya, 1963; Popov *et al*., 1971; Arustamyan, 1972). Skin absorption is more rapid when DNOC is applied in an oily formulation rather than in aqueous solution, peak plasma concentration is higher and occurs earlier (Fabreguettes, 1993, cited in WHO, 2000), indicative of a solvent effect on skin penetration. Biological monitoring of DNOC in blood has been used extensively in cases of acute accidental exposure in humans, as blood levels provide the most reliable indicator of the dose:response relationship for DNOC (DFG, 1998, WHO, 2000). Measurement of atmospheric levels of DNOC is less predictive of possible health effects because of the ready absorption of DNOC through the skin. Absorbed DNOC is preferentially bound to serum proteins and accumulation in blood may occur in man following repeated exposure (Thiele *et al*., 1981; Jastroch *et al*., 1978). Plasma levels increased daily in 18 sprayers exposed to DNOC over a spraying season, and at the end of the season ranged from 11 to 88μg/ml (van Noort, 1960).
>
> "The major metabolic route in the rat and the rabbit following oral administration is by reduction to 6-amino-4-nitro-o-cresol (6-ANOC, 10–12% of administered dose) and, to a lesser extent, to 4-amino-6-nitro-o-cresol (**4-ANOC**), 4-ANOC conjugates and other minor metabolites (Leegwater *et al*., 1982; van der Graaf & Leegwater, 1983). Ingebrigtsen and Froslie (1980) demonstrated rapid reduction to 6-ANOC followed by further reduction to diamino-o-cresol (DAOC) in an *in vitro* study in the presence of rat caecal contents, indicating a metabolic role for intestinal flora. No information is available on metabolic pathways following dermal or inhalation exposure.
>
> "The major route of elimination is in the urine, with a half life in the rat of between 24 and 36 hours following oral administration of 0.4mg/kg body weight (bw) (Leegwater *et al*., 1982). A shorter half life of 6.5 hours has been reported in the rabbit (WHO, 2000). Excretion is reported to be slower in humans (Pollard & Filbee, 1951), and half lives ranging from 4 days (van Noort, 1960) to over 6 days (Pollard & Filbee, 1951; Jastroch *et al*., 1978) have been reported in heavily exposed workers." (Reference cited in SCOEL, 2004).

The ATSDR review of 4,6-dinitro-*o*-cresol summarised the mechanistic data for toxicity:

> "Evidence from one study suggests that DNOC (rather than a metabolite) is the putative toxic agent (Smith *et al*. 1953). Results of genotoxicity studies indicate that DNOC is more genotoxic in the absence (rather than the presence) of exogenous metabolic activation systems. Acute toxic effects are related to DNOC acting directly on cell metabolism and interfering with oxidative phosphorylation. DNOC is believed to cause an acceleration of metabolic processes that are part of the tricarboxylic acid (**TCA**) cycle (Parker *et al*. 1951). During the TCA cycle, the energy produced from the catabolism of glucose is stored in the form of ATP. DNOC produces its accelerative effect by interrupting the phosphate transfer to adenosine diphosphate (**ADP**) to form ATP. Uncoupling allows electron transport to proceed unchecked even when ATP synthesis is inhibited. As a consequence, more ADP and inorganic phosphate are available to drive the TCA cycle, and most of the energy produced from catabolism of glucose is not stored in high-energy phosphate bonds as ATP, but is given off as heat (Parker *et al*. 1951). If heat production exceeds the capacity for heat loss, fatal

hyperthermia may result (Murphy 1986). Signs of DNOC toxicity such as hyperthermia, tachycardia, increased respiration and basal metabolic rates, perspiration, cataractogenesis, and death in humans and animals are related to the uncoupling of oxidative phosphorylation. Several case reports have described the occurrence of elevated body temperatures and complaints of excessive perspiration from employees and patients exposed to DNOC (Bidstrup *et al*. 1952; Plotz 1936; Pollard and Filbee 1951; Stott 1956)." (References cited in ATSDR, 2018).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows 4,6-dinitro-*o*-cresol 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
	mg/m³	mg/m³
Australia	0.2	
Austria	0.2	0.4
Belgium	0.2[1]	
Canada – Ontario	0.2	
Canada – Québec	0.2	
Denmark	0.2	0.4
Finland	0.2	0.6[2]
France	0.2	
Hungary	0.2	0.8
Latvia	0.05	
People's Republic of China	0.6	
Poland	0.05	0.4
Romania	0.05	0.2[2]
South Korea	0.2	
Spain[3]	0.2	
Switzerland	0.2	0.4
USA – NIOSH	0.2	
USA – OSHA	0.2	
UK[4]	0.2	0.6

TABLE 3:
Exposure standards for 4,6-dinitro-*o*-cresol from around the world

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on 4,6-dinitro-*o*-cresol were ACGIH®,SCOEL and Safe Work Australia.

[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] **skin, sen**

[4] The UK Advisory Committee on Toxic Substances considers health may not be adequately protected because of doubts that the limit was not soundly-based. These **OEL**s were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list.

5.2 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review recommended a **TLV-TWA** of 0.2mg/m³ for occupational exposure to 4,6-dinitro-*o*-cresol to minimise the potential for disruption of metabolic processes and metabolic rate that can lead to elevated body temperature (hyperpyrexia), headache, and malaise (ACGIH®, 2019). The ACGIH® review noted that 4,6-dinitro-*o*-cresol can accumulate in the body and blood from excessive, repeated exposure (ACGIH®, 2019).

The rationale for their conclusions included:

> "DNOC causes an increase in metabolic rate that results in elevated body temperature (hyperpyrexia). Severe exposure may cause coma and death. Exposure also causes a yellow pigmentation of the skin, hair, sclera, and conjunctivae. A TLV-TWA of 0.2mg/m³, measured as inhalable fraction and vapor, is recommended to prevent the onset of debilitating symptoms of DNOC intoxication. DNOC should be measured as inhalable fraction and vapor as it exerts sufficient vapor pressure such that it may be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA. The Skin notation is recommended since lethal doses can be absorbed through the skin. Sufficient data were not available to recommend SEN or carcinogenicity notations or a TLV-STEL." (References cited in ACGIH®, 2019).

5.3 SCOEL

The Scientific Committee on Occupational Exposure Limits (SCOEL) assessment of 4,6-dinitro-*o*-cresol concluded that it was not possible to derive a scientifically-based occupational exposure limit in air for 4,6-dinitro-*o*-cresol (SCOEL, 2004).

The rationale for their conclusions included:

> "Consideration of the appropriateness of deriving a health-based occupational exposure limit for DNOC in air is complicated by the importance of the contribution of dermal exposure to total body burden of DNOC, as reported in many studies. Additionally, there are no adequate inhalation studies in animals which would enable derivation of an air concentration which can be considered to be a clear NOAEL. The data on concentrations in air resulting in systemic health effects in workers exposed to DNOC are not also considered adequate or sufficient for derivation of an atmospheric occupational exposure limit.
>
> "Biological monitoring of DNOC in blood has been used extensively in cases of acute accidental exposure in humans, as blood levels provide the most reliable indicator of the dose:response relationship for DNOC (DFG, 1998, WHO, 2000). A threshold of 30–40µg/ml (30–40mg/l) for clinical symptomology of DNOC toxicity has been suggested (WHO, 2000), based on reports from early occupational poisoning cases such as those of Jastroch *et al* (1978) and Steer (1951). While Jastroch and co-workers demonstrated a positive relationship between DNOC levels in blood and the severity of effects, the small numbers involved in the study and limitations in the data do not allow definite conclusions to be drawn about a possible Lowest-Observed-Adverse-Effect-Level (LOAEL) or a No-Observed-Adverse-Effect-Level (NOAEL) for DNOC in blood. It is generally assumed that a DNOC level of up to 10µg/ml (DFG, 1998) or even 20µg/ml (WHO, 2000) is unlikely to result in adverse health effects in humans.

> "While recognising that the genotoxicity data on DNOC give rise to residual concern, SCOEL considers that a biological limit value (**BLV**) of 10µg/ml DNOC in whole blood will be protective of the health of workers who might be exposed to the substance, despite the weakness of the database supporting this level. This is appropriately measured at end of shift, and is proposed as an average value rather than a ceiling limit.
>
> "SCOEL considers, however, that it is not possible to derive a scientifically-based occupational exposure limit in air.
>
> "A "skin" notation is additionally recommended as percutaneous absorption is likely to considerably increase the total body burden. Although DNOC is a skin sensitiser in animals, there are no data which indicate that it has either a respiratory or a skin sensitising potential in humans, nor are there reports of irritancy to the respiratory tract." (References cited in SCOEL, 2004).

5.4 Safe Work Australia

Safe Work Australia proposed a TWA of 0.2mg/m^3 to protect for the accumulation of dinitro-*o*-cresol in the blood and the disruption of metabolic processes and metabolic rate that can lead to elevated body temperature, headache and malaise in exposed workers (Safe Work Australia, 2019). A skin notation was also is recommended based on evidence of dermal absorption and systemic effects in humans.

Their rationale was:

- Dinitro-*o*-cresol (DNOC) is a cumulative poison in humans that is absorbed through the skin.
- Limited toxicological data exists.
- Critical effects include metabolic processes and hyperpyrexia. There are reports of death from exposure in manufacturing of DNOC and in agricultural workers. Symptoms of poisoning include emesis and headache, jaundiced skin, especially on the limbs, tachypnoea, weak heartbeat and severe general depression. Industrial reports noted non-fatal intoxication from exposure to 4.7mg/m^3 with no difficulties reported in workers at 2.5mg/m^3 (ACGIH, 2018). (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne 4,6-dinitro-o-cresol

According to the ACGIH®, DNOC should be measured as inhalable fraction and vapour as it exerts sufficient vapour pressure such that it may be present in both particle and vapour phases, with each contributing a significant portion of the dose at the TLV-TWA.

A method that has been referred to in references is NIOSH Method S166. This method appears to be no longer available. The method used a filter and a midget bubbler in series to collect the sample. In the absence of the NIOSH, or any other method, it may be feasible to analyse samples using a method for water samples such as US EPA method 625 ‘Semi-volatile organic compounds’ by GCMS.

7.0
Discussion

WorkSafe's WES for 4,6-dinitro-*o*-cresol has been unchanged since adoption in 2002.

The toxicological database reviewed above indicates 4,6-dinitro-*o*-cresol is locally and systemically toxic to humans, causing skin, hair and eye staining, and hyperpyrexia, liver and kidney effects; and is locally and systemically toxic to laboratory species. 4,6-Dinitro-*o*-cresol is more toxic to humans than experimental animals, and has the potential to accumulate in repeatedly exposed individuals.

Based on the aforementioned documentation, informed by the conclusions of the ACGIH® and SCOEL reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 0.2mg/m³ for inhalable fraction of 4,6-dinitro-*o*-cresol to be inadequate to manage health risks from possible workplace exposure:

- 4,6-Dinitro-*o*-cresol is more toxic to humans than experimental animals and has the potential to accumulate in exposed individuals, due to the [slower] rate of elimination by humans (ACGIH®, 2019; SCOEL, 2004).
- 4,6-Dinitro-*o*-cresol has the potential to induce skin, hair and eye staining, and hyperpyrexia, and liver and kidney effects in exposed workers (SCOEL, 2004; NIOSH, 2015).
- The stimulation of BMR and subsequent effects can be exacerbated by heat stress (NIOSH, 2015).
- The mutagenic potential of 4,6-dinitro-*o*-cresol is equivocal (WHO EHC, 2000).
- The mechanism(s) by which 4,6-dinitro-*o*-cresol induces toxicity is largely due to the substance's capacity to uncouple oxidative phosphorylation so that energy derived from food is lost as heat and not stored as ATP, producing secondary toxic effects (ATSDR, 2018).
- Limited data from exposed individuals indicated that adverse symptoms were unlikely at whole blood levels of 4,6-dinitro-*o*-cresol below 10–20mg/L (ACGIH®, 2019; SCOEL, 2004; WHO EHC, 2000). However, there is no robust data to extrapolate concentrations of 4,6-dinitro-*o*-cresol in air to blood levels or other biomarkers, and given the potential for dermal absorption, such an OEL in air may not be protective (SCOEL, 2004; DFG, 1998).
- WorkSafe notes the lack of any recent robust data to facilitate setting a WES.
- The most robust dose-response data for 4,6-dinitro-*o*-cresol comes from studies of oral use as a weight-loss product in the US, 1933-1938 (US EPA, 2010).
- The US EPA review of 4,6-dinitro-*o*-cresol in their derivation of provisional subchronic and chronic oral RfD values noted as their POD, the LOAEL of 0.8mg/kg b.w./day for 4,6-dinitro-*o*-cresol induced metabolic and ocular effects in exposed individuals (Ibrahim *et al*., 1934 cited in US EPA, 2010).

- Based on the above LOAEL, a POD of 0.009mg/kg b.w./day can be derived with uncertainty factors of 10 to account for using a LOAEL not NOAEL; of 3 to account for inter-individual susceptibilities; and, of 3 to account for the limitations of the database [the US EPA proposed **UF**s to 1,000]. With direct transformation into an air concentration (route-to-route extrapolation) a dose of 0.009mg/kg b.w./day corresponds to 0.05mg/m^3 [rounded], assuming a body weight of 70kg, a breathing volume of 10m^3 during an eight-hour exposure and 100% absorption.
- The ACGIH® proposed an TLV-TWA for 4,6-dinitro-*o*-cresol at 0.2mg/m^3, but no POD was cited (ACGIH®, 2019).
- The DFG withdrew their MAK Value of 0.2mg/m^3 for 4,6-dinitro-*o*-cresol due to lack of robust data (DFG, 1998).
- The SCOEL determined not to set an OEL due to the lack of robust data and the significance of any potential dermal exposure (SCOEL, 2004).
- The UK **HSE** has removed the OELs for 4,6-dinitro-*o*-cresol, TWA at 0.2mg/m^3 and STEL at 0.6mg/m^3 as *health may not be adequately protected because of doubts that the limit was not soundly-based* (IFA, 2019; UK HSE, 2018).
- The ACGIH® noted that their proposed TLV-TWA for 4,6-dinitro-*o*-cresol at 0.2mg/m^3 was to apply to measured inhalable fraction and vapour as the vapour pressure of 4,6-dinitro-*o*-cresol indicated that both phases could contribute to total dose (ACGIH®, 2019).

Overall:

- The WES-TWA is recommended at 0.05mg/m^3, based on the most robust POD available and acknowledging the uncertainties in the limited database, and noting the results reported by Jastroch *et al*. (1978 cited in SCOEL, 2004).
- A WES-STEL is probably not justified for 4,6-dinitro-*o*-cresol, as at the level of the recommended WES-TWA, cumulative exposures appear to be more critical than short-term peak exposures.
- A skin notation is justified for 4,6-dinitro-*o*-cresol, based on potential exposure contribution, and reported systemic toxicity after dermal administration (SCOEL, 2004).
- Available information indicates that while 4,6-dinitro-*o*-cresol is a dermal sensitiser in experimental animals, there is insufficient evidence about respiratory sensitisation, so a sen notation is not warranted (ACGIH®, 2019; SCOEL, 2004).
- A **BEI** for 4,6-dinitro-*o*-cresol should be investigated as it would give greater worker protection from occupational exposures of 4,6-dinitro-*o*-cresol than air-based OELs, as: whole blood levels of 4,6-dinitro-*o*-cresol below 10–20mg/L are considered to be a robust NOAEL for exposed individuals; dermal exposures to 4,6-dinitro-*o*-cresol have the potential to contribute significantly to total body burden in exposed workers; and, 4,6-dinitro-*o*-cresol can accumulate in exposed individuals.

8.0
Recommendations

WorkSafe considers its current WES-TWA of 0.2mg/m^3 for inhalable fraction of 4,6-dinitro-*o*-cresol with a skin notation 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 4,6-dinitro-*o*-cresol of 0.05mg/m^3, inhalable fraction and vapour
2. retain the *skin notation* for 4,6-dinitro-*o*-cresol.

Noting that the recommended WES-TWA of 0.05mg/m^3 for 4,6-dinitro-*o*-cresol may not eliminate all risk, due to the impact of dermal absorption, and the uncertainties in the [old] database, so exposures should be minimised particularly if heat stress could also be an issue.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
3H-TdR	Tritiated thymidine.
4-ANOC	4-Amino-6-nitro-o-cresol.
6-ANOC	6-Amino-4-nitro-o-cresol.
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.
ADP	Adenosine diphosphate.
ASAT/AST	Aspartate Aminotransferase.
ATP	Adenosine triphosphate.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BEI	Biological Exposure Index.
BLV	Biological Limit Value.
BMR	Basal metabolic rate.
DAOC	Diamino-*o*-cresol.
DEREK	Deductive Estimation of Risk from Existing Knowledge software modelling structure activity relationships.
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.
DGUV-IFA	Deutschen Gesetzlichen Unfallversicherung ([German Social Accident Insurance] – Institut für Arbeitsschutz [Institute for Occupational Safety and Health].
DNOC/DNC	4,6-Dinitro-*o*-cresol.
EHC	Environmental Health Criteria – a World Health Organization program.
EPA	The New Zealand Environmental Protection Authority.
F1	First filial generation.
HPBL	Human peripheral blood lymphocyte.
hprt; HPRT; HGPRT	Hypoxanthine phosphoribosyltransferase or hypoxanthine-guanine phosphoribosyltransferase gene that codes for the enzyme.
HSE	Health and Safety Executive, UK.
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].
IgG	Immunoglobulin G.
IgM	Immunoglobulin M.

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, 2009b). *(cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
LD_{50}	Lethal Dose for 50% of the test population.
LOAEL	Lowest Observed Adverse Effect Level.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg b.w./mg/kg bw	Milligram of substance per kilogram body weight.
mg/kg b.w./ day mg/kg bw/d	Milligram of substance per kilogram body weight per day (exposure rate).
mg/L	Milligram of substance per litre.
mg/m^3	Milligrams of substance per cubic metre of air.
Mutagen Category 2 [pre-2008, Cat. 3]	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. EU term. [H341]
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.
NLM	National Library of Medicine, administered by the US National Institutes of Health.
NOAEL	No Observed Adverse Effect Level.
NOEL	No Observed Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OEL	Occupational Exposure Limit (same meaning as a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
ppm	Parts of vapour or gas per million parts of air.
POD/PoD	Point of Departure. A point on the dose/response curve for the critical adverse effect from which the OEL is extrapolated.
RfD	Reference Dose.
RoC/ROC	Report on Carcinogens.
SCE	Sister Chromatid Exchange.
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.

TERM	MEANING
sen	A substance that can 'sensitise' the skin or 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 term WorkSafe also uses.
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 term WorkSafe also uses.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
SK:SEN	Skin notation indicating the potential for immune-mediated reactions following exposure of the skin. A NIOSH term.
STEL	Short-Term Exposure Limit. 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_3	Triiodothyronine.
T_4	Thyroxine.
TCA	Tricarboxylic acid [cycle].
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.
UDS	Unscheduled DNA Synthesis.
UF	Uncertainty factor.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-STEL	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

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