Workplace Exposure Standard (WES) review

3,5-DINITRO-O-TOLUAMIDE
(DINITOLMIDE)
(CAS NO: 148-01-6)

September 2021

Te Kāwanatanga o Aotearoa
New Zealand Government

WORKSAFE
Mahi Haumaru Aotearoa

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for 3,5-dinitro-*o*-toluamide should be changed.

It considers the potential for exposures to 3,5-dinitro-*o*-toluamide in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for 3,5-dinitro-*o*-toluamide (dinitolmide), which is currently set at a **WES-TWA** of 5 **mg/m³**, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 12th Ed., November 2020 (WorkSafe, 2020).

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

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

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: Dinitolmide; 1-Methyl-3,5-dinitrobenzene; 2-Methyl-3,5-dinitrobenzamide; 3,5-DNT.

2.0 Chemical and physical properties

3,5-Dinitro-*o*-toluamide is a yellowish, crystalline solid at room temperature (**NLM** PubChem, 2020; **ACGIH**®, 2007).

CheChemical and physical properties of 3,5-dinitro-*o*-toluamide include:

Formula	$C_8H_7N_3O_5$
Molecular weight	225.16 g/mol
Physical form	Yellowish, crystalline solid
Melting point	177°C
Vapour pressure	6.78 x 10^{-8} torr at 25°C
Solubility	Water: very slightly soluble; soluble in acetone, acetonitrile, dioxane, and dimethyl formamide

NLM PubChem, 2020; ACGIH®, 2007

TABLE 1:
Physicochemical properties of 3,5-dinitro-*o*-toluamide

Health-related hazard classifications for 3,5-dinitro-*o*-toluamide:

SUBSTANCE	CAS NUMBER	CLASSIFICATION
Dinitro-*o*-toluamide	148-01-6	6.1D (All); 6.1D (O); 6.3A; 6.4A; 6.6B

TABLE 2:
HSNO health-related hazard classifications 3,5-dinitro-*o*-toluamide (**EPA**, 2020)

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

[All] Overall classification for that endpoint.
[O] Oral exposure route.
[D] Derman exposure route.
[I] Inhalation exposure route.

3.0
Uses

3,5-Dinitro-*o*-toluamide is used as a coccidiostat (an antimicrobial medicine) and as a feed additive for poultry (NLM PubChem, 2020; ACGIH®, 2007; **NIOSH**, 1995).

Occupational exposure to 3,5-dinitro-*o*-toluamide can occur during production, storage, transportation and end-use.

Workers can be exposed to 3,5-dinitro-*o*-toluamide dust and solutions via inhalation.

The number of workers exposed or potentially exposed to 3,5-dinitro-*o*-toluamide in New Zealand workplaces is unknown.

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the toxicity in exposed humans:

> "In a study of additives to poultry feeds, including nitrofurans, two cases of occupational contact eczema were found in two female poultry attendants. Positive skin reactions were found with Zoalene® (Kozlar and Sesevicka, 1971).
>
> "In a 50-person human patch test, 3,5-dinitro-*o*-toluamide was neither a primary skin irritant nor a skin-sensitizing agent (Wolf, 1958)." (References cited in ACGIH®, 2007).

The New Zealand EPA classifies 3,5-dinitro-*o*-toluamide as a 6.1D, 6.3A. 6.4A and 6.6B substance – a substance that is acutely toxic, irritating to the skin, irritating to the eye and is a suspected human mutagen respectively (EPA, 2020).

Animals

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the acute toxicity in experimental animals:

> "3,5-Dinitro-*o*-toluamide is of moderate, acute oral toxicity when tested in rats, with an **LD_{50}** of 600 **mg/kg** (Sunshine, Edit., 1969). In the dog, the intravenous LD50 was 75 mg/kg (Topeka, 1966). Neither reference included information around clinical signs following overdosing. Single doses of 150 mg/kg caused methemoglobin formation in rats (Goslin *et al*., 1984)." (References cited in ACGIH®, 2007).

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the irritation/corrosion potential in experimental animals:

> "3,5-Dinitro-*o*-toluamide (2 production samples tested) was only slightly irritating to rabbit eye and skin (Olson, 1960)." (References cited in ACGIH®, 2007).

No data was available on the sensitisation potential of 3,5-dinitro-*o*-toluamide in experimental animals.

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the repeat dose toxicity in experimental animals:

> "Rats were fed either 30, 100, 300, 1,000, or 3,000 **ppm** (3, 10, 30, 100, or 300 mg/kg) 3,5-dinitro-*o*-toluamide for 90 days (Lockwood, 1957). No effects were seen in male rats fed 100 ppm or in female rats fed 300 ppm. Testes were small with degeneration of tubules with replacement fibrosis as seen at both 1,000 and 3,000 ppm with trace lesions seen at 300 ppm. At 1,000 and 3,000 ppm, focal necrosis of the liver and degeneration of the tubular epithelium of the kidney was seen in the male rats. Females fed 3,000 ppm, but not 1,000 ppm, had cloudy swelling, vacuolation, and necrosis of renal tubular epithelium. Body weights were reduced at ≥ 300 ppm in males and at ≥ 1,000 ppm in females. Polychromatophilia and a tendency toward decreased haematocrit were also seen only in males fed 3,000 ppm (Lockwood, 1957).

> "No adverse effects were seen in beagle dogs fed either 65, 125, or 250 ppm for 1 year (approximately daily dose of 1.5, 3, or 6 mg/kg) (McCollister, 1963a). Four puppies were born to one of the 125-ppm females. The puppies appeared normal and showed no gross or microscopic pathologic changes when sacrificed after 6 months of receiving diet containing 125 ppm 3,5-dinitro-*o*-toluamide (McCollister, 1963a)." (References cited in ACGIH®, 2007).

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the reproductive and developmental toxicity in experimental animals:

> "Groups of male and female rats were fed diets of 0, 31, 62, or 125 ppm through two generations, two litters per generation. There was no evidence of an adverse effect on fertility, gestation, viability or lactation (McCollister, 1963b)." (Reference cited in ACGIH®, 2007).

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised genotoxic potential in experimental animals and *in vitro* test systems:

> "3,5-Dinitro-*o*-toluamide was mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, both with and without metabolic activation, and it was also positive in *Escherichia coli* WP2 (Shirasu *et al*., 1978). The same investigators found the chemical active in *Bacillus subtilis* and a second *E. coli* strain (Ohta *et al*., 1980). Activity was felt to be restricted to organisms unable to synthesize ultraviolet-specific endonuclease as a series of organisms (*Sachormyces cerevisiae*, *E. coli, pneumoniae*) with this enzyme showed no mutagenic response (Voogd, 1978). There were no nonbacterial tests or *in vivo* mammalian tests available to evaluate the genotoxicity of 3,5-dinitro-*o*-toluamide." (References cited in ACGIH®, 2007).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] has no evaluation on the carcinogenic potential of 3,5-dinitro-*o*-toluamide (IARC, 2020).

The US National Toxicology Program [**NTP**] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of 3,5-dinitro-*o*-toluamide (NTP RoC, 2016).

The New Zealand EPA has not classified 3,5-dinitro-*o*-toluamide as a 6.7A or 6.7B substance – substances that are known or presumed, or suspected human carcinogens, respectively (EPA, 2020).

Humans

No data was available on the exposure and carcinogenicity potential of 3,5-dinitro-*o*-toluamide in humans.

Animals

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the data on exposure and carcinogenicity in experimental animals:

> "Male and female rats were fed 3,5-dinitro-*o*-toluamide at dietary concentrations of 0 (control), 15, 31, 62, or 125 ppm (equivalent to daily intakes of approximately 0, 0.8, 1.5, 3, or 6 mg/kg) for 2 years (McCollister, 1963b). No adverse responses were seen following feeding up to 62 ppm including general appearance and behaviour, growth, mortality, hematology, and pathology (organ weight, gross and microscopic examinations) were detected in 3,5-dinitro-*o*-toluamide-treated rats. At 125 ppm, slight liver weight increases in females and a slight increase in fatty vacuoles in the liver of both sexes was seen. No increase in tumors was seen (McCollister, 1963b)." (References cited in ACGIH®, 2007).

4.3 Absorption, distribution, metabolism and excretion

The ACGIH® review of 3,5-dinitro-*o*-toluamide summarised the absorption, distribution, metabolism and excretion (**ADME**):

> "In chickens, 3,5-dinitro-*o*-toluamide is metabolized by reduction of either nitro group, followed by partial amide hydrolysis. The primary products are 3-amino-5-nitro-o-toluamide, 5-amino-3-nitro-o-toluamide, and 3-amino-5-nitrotuloic acid. The parent compound and its metabolites are rapidly eliminated via the feces (Goslin *et al*., 1984)." (References cited in ACGIH®, 2007).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows 3,5-dinitro-*o*-toluamide exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2020).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia		5		
Austria		5[1]		10[1]
Belgium		1		
Canada – Ontario		1		
Canada – Québec		5		
France		5		
Ireland		1		
New Zealand		5		
South Korea		5		
Spain		5		
Switzerland		5[1]		
USA – NIOSH		5		

TABLE 3: Exposure standards for dinitolmide 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 3,5-dinitro-*o*-toluamide were ACGIH® and Safe Work Australia.

5.2 ACGIH®

The American Conference of Governmental Industrial Hygienists (ACGIH®) review of 3,5-dinitro-*o*-toluamide concluded with recommendations that a **TLV-TWA** of 1mg/m³ for occupational exposure to 3,5-dinitro-*o*-toluamide, would minimise the potential for liver damage and other unwanted effects (ACGIH®, 2007).

Rationale:

> "A TLV-TWA of 1mg/m³ should be sufficient to protect against the adverse effects of 3,5-dinitro-*o*-toluamide. This number derives from a no-observed effect level (**NOEL**) of 3mg/kg in a 2-year rat study (McCollister, 1963b), supported by a 6mg/kg NOEL in a 1-year dog study (McCollister, 1963a). There is a relatively limited database for this chemical: the testes (as well as the liver and kidney) are the target organ(s) in the rat and chicken at higher doses, the material is genetically active in bacterial systems, and no specific inhalation data are available. An A4, **Not Classifiable as a Human Carcinogen**, is assigned. There were insufficient data to establish either a **Skin** or a **SEN** notation or recommend a **TLV-STEL**." (References cited in ACGIH®, 2007).

[1] Inhalable aerosol.

5.3 Safe Work Australia

Safe Work Australia has recommended an 8-h **TWA** of 1mg/m^3 for 3,5-dinitro-*o*-toluamide to protect for liver damage in exposed workers.

Safe Work Australia state that "This TWA is expected to be protective of liver damage reported in animals." (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne 3,5-dinitro-*o*-toluamide

“WorkSafe is currently unaware of methodology available for determining worker exposure to 5-dinitro-*o*-toluamide.

The unavailability of such a method should be taken into account in any health risk assessment for workers who may be exposed.”

7.0
Discussion

WorkSafe's WES for 3,5-dinitro-*o*-toluamide has been unchanged since adoption in 1994.

The very limited toxicological database reviewed above indicates that 3,5-dinitro-*o*-toluamide may be locally toxic to humans, causing contact eczema. 3,5-Dinitro-*o*-toluamide is systemically toxic to experimental animals, causing liver, kidney and testes damage in rats.

Based on the aforementioned documentation, informed by the conclusions of the ACGIH® review and in particular the findings listed below, WorkSafe considers its current WES-TWA of 5 mg/m³ for 3,5-dinitro-*o*-toluamide, to be inadequate to manage health risks from possible workplace exposure:

- 3,5-Dinitro-*o*-toluamide is a potential toxicant in exposed workers as it may induce contact eczema, with the possibility of liver, kidney and testes damage based on the results from animal testing (ACGIH®, 2007).
- The ACGIH® review of 3,5-dinitro-*o*-toluamide concluded with recommendations that a TLV-TWA of 1 mg/m³ would minimise the potential for liver damage and other unwanted effects. The TLV-TWA was based on a **NOAEL** of 3 **mg/kg b.w./day** from a 2-year dietary study in rats, and adjusted to an inhalation equivalent with uncertainty factor(s) (ACGIH®, 2007).
- The Safe Work Australia draft review of 3,5-dinitro-*o*-toluamide recommended a TWA of 1 mg/m³, to protect for liver damage in exposed workers (SafeWork, 2019).
- A ***skin*** notation is not justified for 3,5-dinitro-*o*-toluamide, due to the absence of reports on the potential significance of dermal absorption from contact with 3,5-dinitro-*o*-toluamide (ACGIH®, 2007).
- Available information indicates that 3,5-dinitro-*o*-toluamide is not a sensitiser (ACGIH®, 2007), and a ***sen*** notation is not warranted.

8.0
Recommendations

WorkSafe considers its current WES-TWA of 5 mg/m^3 for 3,5-dinitro-*o*-toluamide to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for 3,5-dinitro-*o*-toluamide of 1 mg/m^3.

Noting that the proposed WES-TWA for 3,5-dinitro-*o*-toluamide may not eliminate all risk, due to the uncertainties inherent from a very limited toxicological database and workplace reports, so workplace exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
≥	Greater than or equal to.
A4 Not Classifiable as a Human Carcinogen	Agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories. An ACGIH® term.
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: https://portal.acgih.org/s/store#
ADME	Absorption, Distribution, Metabolism and Excretion.
EPA	The New Zealand Environmental Protection Authority.
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].
LD_{50}	Lethal Dose for 50% of the test population.
mg/kg	Milligrams per kilogram.
mg/kg b.w./day	Milligram of substance per kilogram body weight per day (exposure rate).
mg/m^3	Milligrams of substance per cubic metre of air.
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.
ppm	Parts of vapour or gas per million parts of air.
Risk criteria	The terms of reference against which the significance of risk is evaluated. It is used to support decision making on health risk management. ISO 31000 2nd edition *Risk Management – guidelines* (2018).
RoC	Report on Carcinogens.
sen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
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®

TERM	MEANING
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
TWA	Time-weighted average exposure.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-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

American Conference of Governmental Industrial Hygienists (ACGIH®). 2007. *3,5-Dinitro-o-toluamide*. Chemical Substances 8th Edition Documentation. Cincinnati, Ohio: ACGIH®. From ACGIH®, Documentation of the Threshold Limit Values and Biological Exposure Indices, 8th Edition. Copyright 2020. Reprinted with permission.

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Notes

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