Workplace Exposure Standard (WES) review

CYANAMIDE
(CAS NO: 420-04-2)

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Te Kāwanatanga o Aotearoa
New Zealand Government

WORKSAFE
Mahi Haumaru Aotearoa

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1.0
Introduction

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

It considers the potential for exposures to cyanamide 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 cyanamide, which is currently set at a **WES-TWA** of 2 **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 WESs to be used as **risk criteria** for health risk assessment and risk management purposes and to be applied or interpreted only by people with appropriate training and experience. The value proposed in this document is considered by WorkSafe to be a health-based WES. This means it is based on minimising health risk and does not take the practicability of achieving or measuring the value into consideration. This also means that in some instances the current analytical or sampling methods will not be sensitive enough to allow measurement at a level sufficiently below the WES to assess risk with a high degree of confidence. In this case, there will be some uncertainty as to whether risk is suitably managed. As with any risk assessment, the uncertainties inherent in the assessment need to be considered and minimised so far as is reasonably practicable through good risk assessment and control.

We consider it critical to set health-based values 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: Hydrogen cyanamide; Amidocyanogen; Carbimide.

2.0 Chemical and physical properties

Cyanamide is a colourless, hygroscopic, deliquescent crystalline solid with no apparent odour at room temperature (**NLM** PubChem, 2020; **ECHA**, 2014; **DFG MAK**, 2007; **ACGIH®**, 2001).

Chemical and physical properties of cyanamide include:

Formula	CH_2N_2
Molecular weight	42.04 g/mol
Physical form	Colourless, hygroscopic, deliquescent crystalline solid
Specific gravity	1.282 g/cm³ at 20°C
Melting point	46°C
Boiling point	Decomposes before boiling at normal atmospheric pressures; 83°C at 0.5 torr
Relative vapour density	1.45 (air = 1)
Vapour pressure	0.5 Pa at 20°C; 1.0 Pa at 25°C
Flash point	140.6°C
Solubility	Water: very soluble; soluble in alcohol and ether
Partition coefficients	$\log K_{OW}$ = -0.82 at 20°C
Conversion factors	1 ppm = 1.72 mg/m³ 1 mg/m³ = 0.58 ppm

NLM PubChem, 2020; ECHA, 2014; **SCOEL**, 2003; ACGIH®, 2001

TABLE 1: Physicochemical properties of cyanamide

Health-related hazard classifications for cyanamide:

SUBSTANCE	CAS NUMBER	CLASSIFICATION
Hydrogen cyanamide	420-04-2	6.1C (All); 6.1C (O); 6.1C (D); 6.1D (I); 6.3A; 6.4A; 6.5B; 6.8B; 6.9A (All); 6.9A (O)

TABLE 2: **HSNO** health-related hazard classifications of hydrogen cyanamide (**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

Cyanamide is used as an intermediate for dicyandiamide in the production of melamine; as a component in plant growth regulators used to promote uniform and increased bud break and flowering of kiwifruit and earlier concentrated flowering of apples, fumigants and metal cleaners; in the refining of ores; in the production of synthetic rubber; and in other chemical syntheses (NLM PubChem, 2020; SCOEL, 2003; ACGIH®, 2001, EPA, 2020b).

Cyanamide and its calcium salt have been used as therapeutic agents for their 'Antabuse-like' effects in the treatment of alcoholics (SCOEL, 2003).

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

Workers can be exposed to cyanamide vapour and liquid via inhalation, and eye and skin contact.

The number of workers exposed or potentially exposed to cyanamide in New Zealand workplaces is unknown.

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The ECHA **CLH** Report on cyanamide noted that no relevant information was located regarding acute toxicity in humans following exposure to cyanamide (ECHA CLH, 2014).

The DFG MAK review of cyanamide noted:

> "In a single-blind study, 10 male volunteers (see Section 3.2) first took 50 **mg** calcium cyanamide or a placebo and 2 hours later 0.25 g ethanol/kg body weight; this procedure was repeated once 5–7 days later. 30 to 60 minutes after alcohol consumption, clinical symptoms occurred in the form of erythema on the face, neck and around the shoulders and back; these were reversible after 120 minutes; the pulse rate was increased and the diastolic blood pressure was reduced. Some of the volunteers also complained about breathing difficulties after deep inhalation following the intake of cyanamide and alcohol; furthermore, some of the persons exposed to cyanamide became pale 3 hours after alcohol consumption and reported headaches (Jones *et al*. 1988)." (Reference cited in DFG MAK, 2007).

The New Zealand EPA classifies cyanamide as a 6.1C and a 6.1D substance – a substance that is acutely toxic (EPA, 2020a).

The ECHA CLH Report on cyanamide summarised the irritation/corrosion potential, but noted that there was no relevant data for eye or respiratory tract irritation/corrosion:

> "Severe irritation can occur in humans after dermal exposure." (ECHA CLH, 2014).

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

The ECHA CLH Report on cyanamide summarised the sensitisation potential in humans:

> "A few cases of dermal sensitisation in humans have been reported. However, based on the information from the cyanamide production Degussa AG (formerly SKW Trostberg AG) that no cases of confirmed or suspected allergy towards cyanamide occurred. Even though these persons were heavily exposed, there is very limited evidence that cyanamide causes skin sensitisation in humans." (ECHA CLH, 2014).

The DFG MAK review of cyanamide noted:

> "In a study of employees from a calcium cyanamide production plant, there were no positive findings among the 29 employees tested in the epicutaneous test with 0.5% cyanamide in water (Mertschenk *et al*. 1991).
>
> "Partly pronounced, presumably allergic skin reactions caused by occupational contact with cyanamide or calcium cyanamide and manifest in the form of (generalized) erythroderma in some cases were described in earlier communications and reviews without giving details of the diagnosis (Castelain *et al*. 1959; Louste and Pinoche 1929; Pautrier *et al*. 1929; Schwartz *et al*. 1957). Recent reports, which have not always been adequately documented, about effects of cyanamide on the skin are associated with its use as aversive medication for alcoholism. Lichen-planus-like changes to the

skin or oral mucosa were sporadically observed (Kawana 1997; Torrelo *et al*. 1990). In one case, treatment with calcium cyanamide led to (generalized) eczematous erythroderma. In a patch test with the calcium cyanamide solution (diluted 1:2 and 1:10) and with 0.5, 1 and 5% cyanamide solutions, the patient showed a clearly positive reaction and a weakly positive reaction to 0.1% cyanamide in water after 96 hours. 20 control persons showed no reaction to a 5% cyanamide solution (Abajo *et al*. 1999). One patient with granulocytopenia possibly induced by cyanamide and with generalized, scaling erythema revealed a reaction to 0.01, 0.1 and 1% cyanamide solutions in an inadequately documented patch test. A positive result was also described for a lymphocyte stimulation test with cyanamide not specified in more detail (Ajima *et al*. 1997).

"Among a total of 7 patients who developed exfoliative dermatitis (6 patients) and a lichen-planus-like eruption (1 patient) resulting from treatment with calcium cyanamide, 6 patients showed weak or pronounced reactions to the 1% cyanamide solution, and some of them exhibited pronounced reactions even to 0.1% and weak reactions to 0.001% cyanamide in water (Kawana 1997).

"Eczematous, sometimes bullous skin changes were also reported among a total of 5 persons who administered or handled solutions containing calcium cyanamide. In these cases, too, the allergic genesis was verified by clearly positive patch test reactions to 1% cyanamide solution or the preparation diluted 1:10 and 1:100 (Conde-Salazar *et al*. 1981; De Corres and Lejarazu 1982; Goday Buján *et al*. 1994). In one of the studies, 35 control persons did not react to 1% cyanamide in water (Goday Buján *et al*. 1994).

"Occupational contact with an anti-rust paint containing lead cyanamide led to vesicular dermatitis in one case. There was a highly positive reaction to 2% lead cyanamide in olive oil in the patch test after 48 and 96 hours (Black 1975). In another case (Calnan 1970), it cannot be stated clearly whether the sensitization observed was due to cyanamide or dicyclohexylcarbodiimide." (References cited in DFG MAK, 2007).

The New Zealand EPA classifies cyanamide as a 6.5B substance – a substance that is a contact sensitiser (EPA, 2020a).

The ECHA CLH Report on cyanamide summarised the repeat dose toxicity in exposed humans:

"Cyanamide exposure (ingestion or inhaltion [sic]) alone when handled improperly or more pronounced in combination with alcohol consumption induces vasomotoric reactions, known as 'Cyanamide Flush'; including several clinical symptoms, for example, facial flushing, tachycardia, dyspnea, hypotensia, headache, nausea, vomiting, tightness in the chest and sensation of coldness in the extremities. In general these symptoms disappear with no residual effects on general health without specific treatment. In the cases of exposure to larger quantities (gram range/day) severe irrritating [sic] properties of hydrogen cyanamide to the mucous membranes were also observed. Additional effects such as trembling, convulsion, salivation, danger of aspiration, pains behind the sternum and in the epigastrum, unconsciousness and final exits can occur. After dermal exposure severe irritation can occur. In the case of poisoning a symptomatic therapy is recommended. No specific antidote is known. The main metabolite of cyanamide, N-acetylcyanamide can be measured in urine samples from humans and is suitable for biomonotoring [sic] purposes.

> "Calcium cyanamide has been worldwide intensively used as drug [sic] to deter drinking in alcoholics. The consumption of alcoholic beverages after intake of cyanamide leads to intolerances. This is probably due to an inhibition of acetaldehyde dehydrogenase thus leading to a retardation in ethanol breakdown which stops on the stage of acetaldehyde accumulating in the blood. Intolerance reactions towards alcohol occur in man after daily cyanamide doses higher than 20 mg. In general daily doses of more than 0.4–1 **mg/kg bw** cyanamide have been used in the alcohol aversion therapy. The duration of the treatment ranges from a few months to a few years. In some cases patients have taken cyanamide for more than 10 years.
>
> "Several Spanish publications reported of abnormal liver histology produced in alcoholic patients who had received cyanamide as aversion therapy. These generally describe 'ground glass hepatocytes', which are not found in normal livers. Two of the reports also suggest that calcium cyanamide may cause actual liver disease. The significance of these cytoplasmic inclusion bodies has not been clarified. It is supposed that it could be due to the effects of excessive ethanol use, raised blood acetaldehyde levels and/or the alcohol deterrent drug. No signs of diseases or health impairments caused by cyanamide were found during medical surveillance on manufactoring [sic] plant personnel. Medical examinations also included special investigations of functional disorders regarding the testes and the thyroid gland and potential sensitising properties." (ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised the reproductive and developmental toxicity in humans:

> "Medical surveillance on manufactoring [sic] plant personnel, which also included special investigations of functional disorders regarding the testes and the thyroid gland and potential sensitising properties, did not reveal any signs of diseases or health impairments caused by cyanamide.
>
> "In a medical examination it was investigated if there are effects of cyanamide exposure on the testes and the thyroid gland. According to this investigation disturbances of the gonadal function and the thyroid function can be excluded (Mertschenk *et al*, 1993)."
>
> "Calcium cyanamide has been worldwide intensively used as drug to deter drinking in alcoholics. Intolerance reactions towards alcohol occur in man [sic] after daily cyanamide doses higher than 20mg. In general daily doses of more than 0.4–1mg/kg bw cyanamide have been used in the alcohol aversion therapy. The duration of the treatment ranges from a few months to a few years. In some cases patients have taken cyanamide for more than 10 years. No signs of reproductive disorders have been observed." (Reference cited in ECHA CLH, 2014).

The New Zealand EPA classifies cyanamide as a 6.8B substance – a substance that is a suspected human reproductive and developmental toxicant (EPA, 2020a).

The ECHA CLH Report on cyanamide noted that no studies were located regarding genotoxicity in humans following exposure to cyanamide (ECHA CLH, 2014).

Animals

The ECHA CLH Report on cyanamide summarised the acute toxicity in experimental animals:

> "The acute oral **LD_{50}** was determined in a former study in rats to be 142 mg/kg bw cyanamide (Engels, 1973). Mortality mainly occurred during the first day after administration. Cyanamide is considered to be toxic via the oral route in this study. Additionally, a modern study was carried out in accordance to a recent guideline under **GLP**. An oral LD_{50} of 223 mg/kg bw cyanamide was obtained. Signs of intoxication included lethargy, hunched posture, uncoordinated movements, tremors, piloerection and breathing difficulties (Daamen, 1994). It is concluded that the study by Daamen (1994) is a reliable study as it was performed according to GLP and **OECD** 401 and thus relevant details and results are provided with the report. The study by Engel (1973) is considered to be of supplementary value for the purpose of classification and labelling. The results of this study cannot be excluded to derive the LD_{50}. Therefore, the oral LD_{50} (sex combined) is considered to be 142–223 mg/kg bw leading to classification and labelling with **T, R25**.
>
> "The dermal LD_{50} was found to be between approximately 2,120–3,180 mg/kg bw of cyanamide in an elder study. In a newer study according to recent guidelines the acute dermal toxicity of an aqueous cyanamide solution was re-examined. Based on the observed mortality pattern in this study, it was concluded that the LD_{50} of pure active substance cyanamide is 848 mg/kg bw combined for the sexes. Therefore, cyanamide is considered to be harmful in contact with skin.
>
> "Although a four hour exposure to 1.0 mg pure active substance cyanamide/L air (the highest attainable concentration) was considered to be supplementary, the study was suitable to determine the **LC_{50}** in rats. No mortality or severe injury was observed. Therefore, the LC_{50} of cyanamide was greater than 1.0 **mg/L** air." (References cited in ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised the irritation/corrosion potential in experimental animals:

> "Three studies were performed to investigate the skin irritating potential of cyanamide. The results were contradictory: a newer study with an aqueous hydrogen cyanamide solution (49% **w/w**) did not show any irritating potential, whereas two elder studies (SKW Cyanamide L 500 and preparation ALZODEF (> 25%)) revealed a skin irritating potential of cyanamide.
>
> "Regarding the dermal effects of the 21-day dermal toxicity study in rats (Murugan, S.S. *et al*. (1996), see section 4.7.1.3) and the result of skin sensitisation by the method of Buehler (Mercier (1988), see section 4.6.1.1), an overall weight of evidence suggests at least a skin irritating potential."
>
> "The potential of cyanamide was examined to cause skin corrosion *in vitro* using EpiDerm™ reconstructed skin membranes (Reus, 2011). ...In comparison to potassuim [sic] hydroxide the results of the assay demonstrated that cyanamid [sic] is corrosive.
>
> "In a skin irritation study similar to OECD **TG** 404 conducted with Cyanamide F1000, well-defined to moderate erythema, slight ischemia, very slight incrustation and very slight edema were observed after 52h. The treated skin areas had a purple colour suggesting the presence of haemorrhages. After one week the greater part of the treated skin areas showed slight to distinct necrosis. Hence the seen effects were not completely reversible with in [sic] the observation period." (References cited in ECHA CLH, 2014).

"Aqueous hydrogen cyanamide 49% w/w was an eye irritant to one New Zealand white rabbit under the test conditions. Due to the severity of the reaction no further animals were exposed to the test substance. In a second study a 50% aqueous dilution of cyanamide (SKW Cyanamide L 500) was irritating to the eyes of six New Zealand white rabbits. One week after the end of exposure some recovery was observed. After 7d, slight conjunctivitis was still noted in all animals." (References cited in ECHA CLH, 2014).

"In the acute (4-hour) inhalation toxicity study in rats with cyanamide no mortalities were recorded during the study. During the exposure a lumback behaviour and a rapid shallow respiration with frequent coughing and swallowing were observed. Within a few hours after exposure all animals were completely recovered and showed normal behaviour. No visible lesions were observed at gross necropsy (Kruysse, 1973).

"In the 14-day inhalation study in Wistar rats, no mortality and no clinical signs of toxicity were observed. There were liver and kidney weight changes in males and females. Histopathological changes revealed consistent recurring lesions in the brain (oedema), liver (centrilobular cloudy swelling, hyperaemia), heart and lungs in the high dose group in both sexes. Bronchiectasis was observed in 2 males and 1 female (5 of each sex) (Kumar *et al*., 1996).

"There is no evidence of respiratory tract irritation in the available studies." (References cited in ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised the sensitisation potential in experimental animals:

"According to the classification by Magnusson and Kligman, cyanamide had skin-sensitising properties: after dermal application of SKW Cyanamide F 1000 (pure active substance) all Albino guinea pigs showed a positive response in the challenge test. According to the method of Buehler an aqueous solution of cyanamide (53% **w/v**) induced some positive skin reactions after the challenge application (4/20). Indications for a severe irritating effect of cyanamide was noticed in one of these rabbits due to histological examination, whereas no histological findings showed any sign of delayed hypersensitivity. Thus, the results of the Buehler test were inconclusive. In contrast, the more sensitive **M&K** test clearly demonstrated a potential for skin sensitisation." (ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised the repeat dose toxicity in experimental animals:

"A short-term oral toxicity study of cyanamide in the rat at doses of 0, 5, 10, 20, 40 **mg/kg bw/day** over a period of 28 days was characterised by a depression in body weight, body weight gain and food consumption at 20 and 40 mg/kg bw/day (Osheroff, 1988). A decrease in red cell parameters was obtained in males and females at the highest dose associated by decreases in **MCH** and **MCHC** and an incidental increase of total bilirubine [sic]. It was assumed that anaemia was caused by haemolysis. Splenic pigmentation in females was found at 10 mg/kg bw/day and higher, which was seen as well in males, but only at the highest dose of cyanamide. Histopathological thyroid findings obtained in the low dose group of male rats were not seen as an adverse effect, whereas the more severe changes at 10 mg/kg bw/day and up were attributed to cyanamide. In females, thyroid effects were obtained at 20 and 40 mg/kg bw/day. Other histopathological findings were seen at 10, 20 and 40 mg/kg bw/day in the liver of males (bile duct hyperplasia). The **NOAEL** for cyanamide was 5mg/kg bw/day, based on the thyroid effects in males at 10 mg/kg bw.

"A 90-day oral toxicity study was performed in rats with 0.5, 1.5 and 4.5 mg/kg bw/day of cyanamide (corresponding to 10, 30, 90 ppm; feeding study) (Til *et al*., 1975). At 4.5 mg/kg bw/day thyroid effects were seen in males as well in females. The changes in the thyroid were comparable to the effects found in the 4 week study. Histopathological changes in the thyroids in only one male (1/20) were not contributed due to an adverse effect of cyanamide at 1.5 mg/kg bw/day. Additionally, male rats showed – in contrast to the 28 day study – a slight increase in erythrocyte counts. The NOAEL was 1.5 mg/kg bw/day pure active substance cyanamide (equivalent to 30 ppm in the diet) in males and females.

"In a 90-day oral study of Til *et al*. (1982), Alzodef was administered via gavage at levels of 0.6, 2.0 and 6.0 mg/kg bw/day of active substance cyanamide to 4 male and 4 female beagle dogs, about 4 months old, per test group over a period of 3 months. Histopathological findings in testes and epididymidis [sic] regarding spermatogenesis accompanied by reduced testes weights were most pronounced at 6 mg/kg bw/day. Slight changes in testes and epididymides [sic] found in the lower dose groups are regarded as findings unrelated to treatment of which degree and incidence disappear within the background. The experts of the PRAPeR Meeting 79 concluded the dose of 0.6 mg/kg bw/day in the 90-day oral study of Til *et al*. (19821) is a **LOAEL**. However, in agreement with the study authors Til *et al*. (1982; TOX2001-425) it seems justified to relate the more severe changes in testes and epididymidis [sic] observed in the high-dose group to the administration of cyanamide, whereas the slight changes found in the lower dose groups are regarded as findings unrelated to treatment of which degree and incidence disappear within the background (discussed in *Conclusion of the Rapporteur Member State (RMS) about the appropriate overall NOAEL for the dog regarding especially the findings in the testes*). In conclusion, the NOAEL in this study is considered to be 0.6 mg/kg bw/d based on decreased **T3** and **T4** in the mid and high dose animals.

"In a supplementary (90 day) oral toxicity study with dogs (Til, H. P. et Beems, R., 1986) 0, 0.6 and 6.0 mg/kg bw/day of cyanamide were administered to mature male beagle dogs (12–15 months at study begin). One of four dogs from the high dose group (6 mg/kg/day) had tubular degeneration/depletion in the testes, sloughed germ cells/debris in the epididymis and reduced sperm in the epididymis. Although these changes could be incidental, their possible relationship to cyanamide administration cannot be excluded. The NOAEL was 0.6 mg/kg bw/day and was based on retarded body weight gain, reduced food consumption as well as evidence on testicular damage at the high dose level of 6 mg/kg bw/day.

"In a 1-year study by Osheroff, M.R. (1989) 0, 0.2, 1 and 5 mg/kg bw/day of cyanamide were administered via oral gavage to 4 beagle dogs of each sex and group (6–8 months old at study begin). It is concluded that the NOAEL of the 1-year study in dog [sic] is 1.0 mg/kg bw/day based on the reduced body weight/gain in both sexes, the haematological findings in the female dogs and the testicular findings in one dog which could not be excluded with certainty as treatment-related.

"A 21-day dermal study in rabbits revealed local skin effects at 25 mg/kg bw and higher after an application of Dormex [a plant growth regulator]. Therefore, the NOAEL for dermal effects was 12.5 mg/kg bw. A NOAEL for systemic effects was not applicable, since the animals were not sacrificed and examined gross pathologically and histopathologically immediately after the end of treatment, but with a period of 14 days after. Data received in pathology and histopathology are not acceptable for evaluation of systemic effects.

"A 14-day inhalation study revealed reduced body weights and body weight gain at 0.15 mg/L air, which was clear dose-dependent in females at higher doses. Thus, the NOAEL was below 0.15 mg cyanamide/L air in this study in rats." (References cited in ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised the reproductive toxicity in experimental animals:

"Three studies on reproduction toxicity in rats are reported, two with substance administration by gavage and one where the test substance was mixed with the feed.

"In the most recent study (Morseth *et al*., 1990) reproductive performance and fertility was affected in **F0** and **F1** parental animals at the top dose group, resulting in a low fertility index in both generations and in an increase of total litter resorptions in the F0 generation.

"In a further study (Obach and Rives, 1985; Rives-Ferriol, 1987), at the high dose level (25 mg/kg bw/d) only, reduced male and female fertility was observed. Unilateral or bilateral testicular atrophy was reported for a few high dose F0 males (4/23).

"In a dietary 2-generation reproduction toxicity study (Koëter *et al*., 1986) cyanamide mating and fertility were found unaffected with the exception of a reduced litter size in the 1st pregnancies of high dose F0 and F1 dams. There was an increased incidence of F1 males with interstitial cell proliferation at the high dose level and tubular atrophy was described in all treated groups. However, only a subset (25%) of the animals at risk for testicular lesions has been examined in this study and there was a lack of a dose-response of the observed changes. Therefore, the testicular findings were not considered to be a reliable basis for risk assessment.

"Testicular findings were observed in repeated dose toxicity studies in dogs, too.

"In a 90-day oral study of Til *et al*. (1982) histopathological findings in testes and epididymidis [sic] regarding spermatogenesis accompanied by reduced testes weights were most pronounced at the highest dose group at 6 mg/kg bw/day in beagle dogs, about 4 months old at study begin. In 2 animals of the high dose group testes atrophy and absent spermatogenesis accompanied by reduced testes weights was observed, whereas no such findings were observed in the 4 control animals. Slight changes in testes and epididymides [sic] found in the lower dose groups are regarded as findings unrelated to treatment of which degree and incidence disappear within the background.

"In a supplementary (90 day) oral toxicity study with dogs (Til, H. P. et Beems, R., 1986) one of four mature male beagle dogs (12–15 months at study begin) from the high dose group (6 mg/kg/day) had tubular degeneration/depletion in the testes, sloughed germ cells/debris in the epididymis and reduced sperm in the epididymis. Although these changes could be incidental, their possible relationship to cyanamide administration cannot be excluded.

"In a 1-year study by Osheroff, M.R. (1989) testicular findings (moderate degeneration of seminiferous tubules in the testes) in one dog (6–8 months old at study begin) at 5 mg/kg bw/day, which could not be excluded with certainty as treatment-related." (References cited in ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised the developmental toxicity in experimental animals:

> "The prenatal developmental toxicity of cyanamide was investigated in rats and rabbits complying to international test guidelines and GLP.
>
> "In rats (Morseth, 1989) signs of prenatal developmental toxicity consisted of reduced foetal weights in the high dose. Foetal weights were also lower in the mid dose group. This is considered relevant because of the lower mean litter size in this group. This would be expected to be associated with an increase in mean foetal weight had the development been unaffected. Foetal morphology was affected at the high dose level presenting an increased incidence of diaphragmatic hernia, isolated cases of skeletal malformations and a variety of skeletal variations.
>
> "In rabbits (Koëter and Marwijk, 1989) dosed with 0, 2, 6 and 18 mg/kg bw/day no indication for teratogenicity was detected in rabbits up to and including the high dose level." (References cited in ECHA CLH, 2014).

The ECHA CLH Report on cyanamide summarised genotoxic potential in experimental animals and *in vitro* test systems:

> "Both Ames-Tests were negative indicating no mutagenic activity in bacterial cells. Two gene mutation assays using mammalian cells were carried out one using mouse lymphoma cells and the other V79-cells.
>
> "A weak positive result was obtained in the mouse lymphoma test at the thymidine kinase locus at the maximum concentrations (1,600 and 1,000 **µg/mL**, respectively), in experiment 1 and 2 without metabolic activation. However, the biological relevance of the observed slight increases is questionable as they were obtained at concentration above and at the level of 10 mM, the limit for mutagenicity tests carried out in cell cultures in order to avoid false positive results due to effects of osmolarity. Therefore the weak mutagenicity in this assay is questionable. Furthermore, no mutagenic effects were obtained at the **HPRT**-locus in V79 with the maximum concentrations of 1,000 and 500µg/mL without **S9** mix and 30 and 250µg/mL with S9 mix.
>
> "Two chromosome aberrations tests in **CHO** cells and in human lymphocytes showed distinct clastogenic effects of cyanamide. In the assay with CHO cells a significant dose-dependent increase in cells with aberrations was obtained with and without metabolic activation at the 20 hour preparation interval. A statistically significant increase in numerical chromosomal aberrations (exclusive gaps) was obtained at the maximum concentrations (33.3µg/mL) without S9 mix and at 33.3 and 333.3µg/mL in the presence of S9 mix in human lymphocytes. Both assays indicate a clastogenic response of cyanamide *in vitro*.
>
> "Three micronucleus assays were carried out in order to investigate the potential of cyanamide to cause chromosomal damage *in vivo*. One assay was performed with male and female Wistar rats, the remaining two with male and female **ICR** mice and Swiss mice, respectively. In the micronucleus assay carried out in the rat only one dose level of calcium cyanamide (153 mg/kg bw) administered via gavage was investigated. The dose was administered twice in an interval of 24h. No increase in micronuclei was obtained. In the two assays carried out in mice the test substance (hydrogen cyanamide and cyanamide Colme, respectively) was administered via gavage and no induction of micronuclei was obtained up to the highest investigated dose (350 and 247mg/kg bw, respectively).

"**DNA** damage and repair was investigated *in vitro* in CHO cells (Sister Chromatid Exchange) and in the **UDS** test in primary rat hepatocytes. In both experiments there was no indication of DNA damage and repair caused by cyanamide. An *in vivo* UDS test was not considered necessary to perform as the weak positive and questionable response in the mouse lymphoma gene mutation test was attributed to clastogenic effects and not to point mutations. This assumption is supported by the negative result of the HPRT-Test in V79 cells.

"The studies cover or exceed all endpoints required for mutagenicity and genotoxicity testing. It is concluded, that cyanamide has a clastogenic potential *in vitro*. However, the clastogenic effects observed *in vitro* could not be detected *in vivo*. Therefore, cyanamide is considered to be not clastogenic *in vivo*." (ECHA CLH, 2014).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] has no evaluation on the carcinogenic potential of cyanamide (IARC, 2020).

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

The New Zealand EPA has not classified cyanamide as a 6.7A or 6.7B substance – substances that are known or presumed, or suspected human carcinogens respectively (EPA, 2020a).

Humans

The ECHA CLH Report on cyanamide noted that no studies were located regarding exposure and carcinogenicity potential in humans (ECHA CLH, 2014).

Animals

The ECHA CLH Report on cyanamide summarised the data on exposure and carcinogenicity in experimental animals:

"Long-term dietary toxicity studies were conducted in rats and mice.

"In the chronic toxicity study in Sprague Dawley rats (Osheroff, 1991) hydrogen cyanamide was administered via oral gavage for 91 weeks. In the high dose group males and females clinical observations demonstrated effects of general debilitation in the health. Due to these observations, the dose levels have been reduced after 16 weeks of treatment. Significant depressions in body weight and body weight gain values are obtained in intermediate and high dose males and females in the first weeks. Mean food consumption revealed significant depression in females and males of the high dose group. Compound-related clinical pathology changes were found in males and females at the high dose group and at males in the intermediate dose group. Compound-related histopatholgical [sic] changes were found in the thyroid of the intermediate and high dose males and at the high dose females. No tumor at any site in the rats could be associated with the administration of the substance. The NOAEL of this study is 1mg/kg/day active substance cyanamide based on the histopathological effects in the thyroid obtained in the intermediate dose. The target organ was the thyroid.

"In a carcinogenicity study, groups of 50 male and female F344 (Fischer) rats (Ulland *et al*., 1979) were administered calcium cyanamide orally in the diet for 107 weeks (control group: 20 animals/sex). No tumour type in the rats could be associated with the administration of the substance.

"In a carcinogenicity study, B6C3F1 mice (dose groups: 50 animals/sex, control group: 20 animals/sex) (Ulland *et al*., 1979) were administered calcium cyanamide orally in the diet for 100 weeks. Significant test substance-related mortalities were found in male mice. Mean body weights of the high dose males and females were slightly lower than those of the corresponding controls. No tumour type in the rats could be associated with the administration of the substance.

"In a carcinogenicity study, [Crl:CD-1 (ICR) BR] mice (Goodyear, 1990) were administered hydrogen cyanamide via the drinking water in concentrations of 70, 200 and 600ppm. A slight increase in morbidity and mortality in the intermediate and high dose females groups was obtained. In the first weeks of the study the body weight gain, the food and water consumption was reduced in the intermediate and high dose groups. Histopathological effects were obtained in the medium and high dose groups evidenced by a dose-related chronic cystitis in the urinary bladder and in the high dose group by atrophic basophilic tubules in the kidney. In females, there was an increased incidence of proliferative lesions in the stromal/luteal tissues of the ovary in the high dose group. The hyperplasias were predominantly of the luteal type, as were the granulosa-theca tumours. The 8 cases of granulosa-theca tumours in group 4 exceeded the range of 0 to 3 cases per group of 51 mice in 10 previous control groups. Statistically, there was a significant dose response trend in granulosa-theca tumours across the 4 groups ($p < 0.01$) regardless of whether the analysis included or excluded equivocal necrotic control case. Pairwise statistical comparison between groups 1 and 4 was significant ($p < 0.05$) if the necrotic control case was excluded but not significant ($p > 0.05$) if this case was included in the analysis. The Maximum Tolerable Dose (**MTD**) was exceeded at the high dose level. There were no treatment-related changes in the tumour profile at 200ppm referring to approximately 12.2mg/kg bw/day active substance cyanamide. The NOAEL was 70ppm referring to approximately 4.2mg/kg bw/day, based on increased mortality, reduction in body weight gain, food consumption and histopathological effects (cystitis (urinary bladder) and atrophic basophilic tubules in kidney) in the mid and high dose." (References cited in ECHA CLH, 2014).

4.3 Absorption, distribution, metabolism and excretion

The ECHA CLH Report on cyanamide summarised the absorption, distribution, metabolism and excretion (**ADME**):

"Studies on the absorption, distribution, metabolism and excretion were conducted with [14C]-radiolabelled test substance in rats (see Table 11). The results from the metabolism study in rats with [14C]-cyanamide demonstrate that the compound is completely absorbed after oral administration and was rapidly excreted. The percent excreted in the urine ranged from approximately 79.0 to 97.7% of the applied dose at 168 hours (faeces 2.76–4.15% and expired **CO_2** 1.45–10%). Regardless of the route of administration a total of approximately 67% to 92% was excreted by all routes in the first 2h postdose. The major metabolic reaction is acetylation of the nitrogen. After oral administration of hydrogen cyanamide, the major urinary metabolite formed in a variety of species, including man, is N-acteylcyanamide [sic]. If at all, other metabolites

seem to play a minor role. A minor biotransformation pathway of cyanamide is the formation of hydroxycyanamide as a product of microsomal oxidation, as shown by *in vitro* studies. Hydroxycyanamide is an intermediate instable [sic] metabolite, which decomposes to cyanide and nitroxyl. However, no metabolic degradation of cyanamide to cyanide was found in men. All tissues (blood, bone, brain, fat, heart, kidneys, liver, lungs, muscle, ovaries, spleen, thyroid and uterus) collected 168h after postdose contained 0.03% or less of the radioactivity, except liver and kidney containing 0.14 to 1.18% and 0.02 to 0.09%, respectively. These results indicated no tendency for accumulation of cyanamide. The half-life ($\mathbf{t_{1/2}}$) of cyanamide is very short with approximately 1h (after **i.v.** administration of 35 mg/kg bw)." (ECHA CLH, 2014).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows cyanamide 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		2		
Austria	0.58[1]	1[1]		
Belgium[2]	0.58	1		
Canada – Ontario		2		
Canada – Québec		2		
Denmark[7]	0.58	1	1.16[6]	2[6]
European Union[3]	0.58	1		
Finland		1		
France[4]	0.58	1		
Germany – **AGS**	0.2[5]	0.35[5]	0.2[5,6]	0.35[5,6]
Germany – **DFG**	0.2[5]	0.35[5]	0.2[5,6]	0.35[5,6]
Hungary		1		
Ireland	0.58	1		
Italy[7]		1		
Latvia	0.58	1		
New Zealand		2		
People's Republic of China		2		
Poland		0.9		1.8
Romania	0.58	1		
Singapore		2		
South Korea		2		
Spain[7]	0.58	1		
Sweden	0.58	1		
Switzerland	0.58	1	1.16	2
The Netherlands		0.2		
Turkey	0.58	1		
USA – **NIOSH**		2		
UK	0.58	1		

TABLE 3: Exposure standards for cyanamide 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 cyanamide were DFG, SCOEL, ACGIH®, and Safe Work Australia.

[1] Inhalable fraction.

[2] 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.

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

[4] Indicative statutory limit values **Skin**.

[5] Inhalable fraction and vapour.

[6] 15 minutes average value.

[7] Skin.

5.2 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] re-evaluation of cyanamide recommended a MAK Value of 0.2 mL/m³ (0.35 mg/m³), **Peak Limitation Category II** (excursion factor 1), with **"H"**, **"Sh"** and **Pregnancy Risk Group C** notations (DFG MAK, 2012; DFG MAK, 2007).

Rationale:

"Statements about the tolerance of cyanamide in humans at the doses used and also in combination with alcohol can be made after its therapeutic use for a limited time as aversive medication to treat alcohol dependence. Results of studies of persons which would allow a scientifically based MAK value to be derived are however not available.

"In a carcinogenicity study, an increase of ovarian granulosa-theca cell tumours was found from 200 mg cyanamide/l drinking water. When one questionable tumour finding in control animals was excluded, the number of granulosa-theca cell tumours in mice of the 600 mg cyanamide/l group was statistically significant. A classification as carcinogen on the basis of only one and, what is more, questionable tumour finding in one control animal does not seem to be justified.

"The testes, thyroid and liver consistently are the target organs of the toxicity of cyanamide in dogs and rats; the liver is also regarded as the target organ in humans and mice. A NOAEL of 0.2 mg cyanamide/kg body weight and day can be derived from a 52-week study in dogs. This results in a value of 1.4 mg cyanamide/m³ in relation to a body weight of 70 kg and the air inhaled of 10 m³ during 8 hours. The MAK value is therefore established at 1 mg cyanamide/m³. Local irritation to humans will presumably not occur at this concentration of cyanamide since the pH corresponds to that of a weak acid. Data from humans for clarifying the irritating effect are urgently required.

"A study on developmental toxicity in rats and rabbits is available. The NOAEL in rats was 15 mg cyanamide/kg body weight and day and that in rabbits was 2 mg cyanamide/kg body weight and day. A sufficient difference from the MAK value for cyanamide of 1 mg/m³ is obtained so that cyanamide is assigned to Pregnancy risk group C.

"Because of the mainly systemic effect and the short half-life, cyanamide is classified in Peak limitation category II with an excursion factor of 2.

"On account of the relatively low dermal LD50 via the skin, cyanamide is designated with H.

"There are several reports on presumably allergic reactions on the skin after ingestion of calcium cyanamide. In some other cases, the repeated topical, sometimes also occupational, exposure to calcium cyanamide led to allergic contact reactions on the skin and positive epicutaneous test reactions to subirritant concentrations of cyanamide. The present findings, which have not always been adequately documented, suggest no pronounced sensitization potential of cyanamide. However, since an animal study with cyanamide using an adjuvant also provided a positive result, cyanamide is designated with Sh.

"Two micronucleus tests *in vivo* did not indicate any clastogenic properties. Cyanamide was not mutagenic *in vitro* in two bacterial mutagenicity tests. No indications which would require a classification of cyanamide in one of the categories for germ cell mutagens have been obtained on the basis of these data." (DFG MAK, 2007).

The change in recommended MAK Value in the 2012 review was due to an additional species-specific correction value regarding the toxicokinetic difference between dog and human of 1: 1.4, applied to the same NOAEL of 0.2 mg/kg b.w./day (DFG MAK, 2012).

5.3 SCOEL

The Scientific Committee on Occupational Exposure Limits (SCOEL) review of cyanamide recommended an 8-hour **TWA** of 1 mg/m^3, with a "skin" notation as percutaneous absorption was expected to significantly increase total body burden (SCOEL, 2003).

Rationale:

> "No reliable data concerning skin, eye and respiratory tract irritation are available. Systemically, cyanamide causes effects related to its ability to inhibit aldehyde dehydrogenase activity, leading to a build-up of acetaldehyde in the concomitant presence of alcohol. It can also produce toxic effects on the liver and other organs, presumably via its metabolites.
>
> "The SCOEL recommendation is based on a NOAEL of 0.2 mg cyanamide/kg bw/day for systemic effects identified in an oral 52-week study in beagles. This dose corresponds to humans being occupationally exposed to a concentration of 1.4 mg/m^3 for 8 hours per day, assuming 100% retention and absorption of inhaled material, a breathing volume of 10 m^3 in 8 hours and a body weight of 70 kg; at this level the effect, if any, of cyanamide on aldehyde dehydrogenase will not have significant health consequences.
>
> "There are no toxicological reasons to specify a particular **STEL** value.
>
> "As there is evidence for significant skin absorption, SCOEL recommends a **Sk** notation.
>
> "Reports on sensitisation upon skin contact and positive reactions in patch testing in humans, which are supported by positive results in animals, indicate that cyanamide should be recognised as a skin sensitiser." (SCOEL, 2003).

5.4 ACGIH®

The ACGIH® review of cyanamide concluded with recommendations that a **TLV-TWA** of 2 mg/m^3 for occupational exposure to cyanamide, would minimise the potential for eye and skin irritation, and provide substantial protection against the undesirable Antabuse effect associated with cyanamide exposure and ethanol ingestion (ACGIH®, 2001).

Rationale:

> "A TLV-TWA of 2 mg/m^3 is recommended for cyanamide. This TLV is considered sufficiently low to minimize skin and eye irritation and is safely below a level that would be necessary to produce an undesirable effect with ethanol ingestion.
>
> "Sufficient data were not available to recommend Skin, **SEN**, or carcinogenicity notations or **TLV-STEL**." (References cited in ACGIH®, 2001).

5.5 Safe Work Australia

Safe Work Australia has recommended an 8h TWA of 0.2mg/m^3 for cyanamide to protect for effects on the male reproductive system and subsequently reduce the potential for irritation effects in exposed workers.

> "Critical effects include local irritant effects and effects on the male reproductive system in mammals" (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne cyanamide

It is acknowledged that currently there are no analytical methods available for the determination of airborne levels of cyanamide.

WorkSafe recommends substituting alternative substances so far as is reasonably practicable.

7.0
Discussion

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

The toxicological database reviewed above indicates that cyanamide is locally and systemically toxic to humans, causing eye and severe skin irritation, and 'Antabuse-like' effects (particularly when combined with alcohol consumption). Cyanamide is locally and systemically toxic to experimental animals, causing severe eye and skin irritation/corrosion, and adverse effects in the male reproductive system.

Based on the aforementioned documentation, informed by the conclusions of the DFG, SCOEL and ACGIH® reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 2 mg/m³ cyanamide, to be inadequate to manage health risks from possible workplace exposure:

- The DFG re-evaluation of cyanamide recommended a MAK value of 0.2 ppm (0.35 mg/m³), Peak Limitation Category II (excursion factor 1), with "H", "Sh" and Pregnancy Risk Group C notations (DFG MAK, 2012; DFG MAK, 2007). The MAK Value was based on a NOAEL of 0.2 mg cyanamide/kg b.w./day from a 52-week study in dogs (DFG MAK, 2007), with a species-specific correction value for the toxicokinetic difference between dog and human (DFG MAK, 2012).
- The SCOEL review of cyanamide recommended an 8-hour TWA of 1 mg/m³, with a "skin" notation as percutaneous absorption was expected to significantly increase total body burden. The TWA was based on a NOAEL of 0.2 mg cyanamide/kg b.w./day from a 52-week study in dogs, with an extrapolation to a human equivalent concentration. SCOEL noted that cyanamide should be recognised as a skin sensitiser (SCOEL, 2003).
- The ACGIH® review of cyanamide concluded with a recommendation that a TLV-TWA of 2 mg/m³ would minimise the potential for eye and skin irritation, and provide substantial protection against the undesirable Antabuse effect associated with cyanamide exposure and ethanol ingestion (ACGIH®, 2001).
- The Safe Work Australia draft review of cyanamide recommended a TWA of 0.2 mg/m³, with **Carc. 2**, Sk., and **DSEN** notations, to protect for effects on the male reproductive system and subsequently reduce the potential for local irritation effects in exposed workers, based on a NOAEL of 0.2 mg cyanamide/kg b.w./day from a 52-week study in dogs (SafeWork, 2019).
- The proposed WES-TWA of 0.2 mg/m³ (aerosol and vapour) of cyanamide is intended to protect exposed workers from potential eye and skin irritation, and effects on the male reproductive system (DFG MAK, 2012).
- A ***skin*** notation appears justified for cyanamide, due to the reported data on the potential significance of dermal absorption from contact with cyanamide (DFG MAK, 2007; SCOEL, 2003).
- Available information indicates that cyanamide is not a respiratory sensitiser, and a ***sen*** notation is not warranted. However, evidence from exposed workers indicates that cyanamide is a potential skin sensitiser (DFG MAK, 2007; SCOEL, 2003).

8.0
Recommendations

WorkSafe considers its current WES-TWA of 2mg/m^3 cyanamide 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 cyanamide of 0.2mg/m^3 (aerosol and vapour)
2. adopt a *skin* notation for cyanamide
3. retain dsen notation for cyanamide.

Noting that the proposed WES-TWA for cyanamide may not eliminate all risk, due to the potential contribution of dermal exposures to total body burden, and the potential for skin sensitisation, so workplace exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and **BEIs®** book and work practice guides. Store at: https://portal.acgih.org/s/store
ADME	Absorption, Distribution, Metabolism and Excretion.
AGS	Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
b.w.; bw	Body weight.
Carc. 2 [pre-2008, Cat. 3]	Carcinogen Category 2: Suspected human carcinogen. EU term.
CHO	Chinese hamster ovary.
CLH	Classification and Labelling Harmonisation – EU program.
CO_2 or CO2	Carbon dioxide.
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.
DSEN	A notation indicating the substance is a dermal sensitiser. DSEN is used in place of SEN when specific evidence of sensitisation by the dermal route is confirmed by human or animal data. An ACGIH® term.
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
F0	Parents to first filial generation, F1.
F1	First filial generation.
GLP	Good Laboratory Practice.
"H"	DFG MAK designation: danger of percutaneous absorption. Equivalent to the skin notation in the WorkSafe WES special guide.
hprt; HPRT; HGPRT	Hypoxanthine phosphoribosyltransferase or hypoxanthine-guanine phosphoribosyltransferase gene that codes for the enzyme.
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.
ICR	Institute of Cancer Research – a constituent college of the University of London
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
IOELV	Indicative Occupational Exposure Limit Value (health-based, SCOEL parameter).
i.v.	Intravenous.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LOAEL	Lowest Observed Adverse Effect Level.

TERM	MEANING
M&K	Magnusson and Kligman (skin sensitisation).
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. Values set by the DFG.
MCH	Mean corpuscular haemoglobin.
MCHC	Mean corpuscular haemoglobin concentration.
µg/mL	Microgram or one millionth of a gram per millilitre.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg b.w. or mg/kg bw	Milligram of substance per kilogram body weight.
mg/kg bw/ day or mg/ kg b.w./day or mg/kg/d	Milligram of substance per kilogram body weight per day (exposure rate).
mg/L or mg/l	Milligram of substance per litre.
mg/m^3	Milligrams of substance per cubic metre of air.
MTD	Maximum tolerated dose.
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.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
Peak limitation category 2 or II	Substances with systemic effects; Excursion factor = 2 [default]; Duration 15 minutes, average value; Number per shift = 4; Interval = 1 hour. A DFG term.
ppm	Parts of vapour or gas per million parts of air.
Pregnancy Risk Group C	Damage to the embryo or foetus is unlikely when the MAK value or the **BAT** value is observed. A DFG term.
R25	Toxic if swallowed.
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.
S9; S-9	Supernatant fraction obtained from an organ (usually liver) homogenate by centrifuging at 9000 g for 20 minutes in a suitable medium; this fraction contains cytosol and microsomes. The microsomes component of the S9 fraction contain cytochrome P450 isoforms (phase I metabolism) and other enzyme activities. The cytosolic portion contains the major part of the activities of transferases (phase II metabolism). The S9 fraction is used in assays to observe the effect of metabolism of drugs and other xenobiotics on the assay endpoint(s).

TERM	MEANING
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
sen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
"Sh"	DFG MAK designation: *danger of sensitisation of the skin*.
"Sk"	SCOEL designation: short-hand for Skin notation.
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	Short-Term Exposure Limit. The STEL is a limit value above which exposure should not occur and usually relates to a 15-minute reference period.
T	Toxic.
$T_{1/2}$ or $t_{1/2}$	Half-life.
T_3	Triiodothyronine.
T_4	Thyroxine.
TG	Test Guideline. An OECD term.
TLV®	Threshold Limit Value [see TLV-STEL and TLV-TWA below]. An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a 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.
UDS	Unscheduled DNA Synthesis.
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.
w/v	Weight per unit volume.
w/w	Weight per unit weight.

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®). (2001). *Cyanamide*. 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.

Deutsche Forschungsgemeinschaft (DFG). (2007). *Cyanamide*. The MAK-Collection Part I: MAK Value Documentations, Vol. 24; pp 75-118. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb42004e0024

Deutsche Forschungsgemeinschaft (DFG). (2012). Cyanamid. The MAK Value Documentation, Vo. 52 in German; pp 1-4. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb42004d0052

Environmental Protection Authority (EPA). (2020a). Chemical Classification and Information Database (CCID): *Hydrogen cyanamide*. www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/view/38C58294-BC13-4BB3-BE31-921DAC2E8C32

Environmental Protection Authority (EPA). (2020b). Decision document for soluble concentrate containing 520 to 540 g/L hydrogen cyanamide. www.epa.govt.nz/assets/FileAPI/hsno-ar/APP203865/APP203865_Final_Decision.pdf

European Chemicals Agency (ECHA) Classification and Labelling Harmonisation (CLH). (2014). *Proposal for Harmonised Classification and Labelling: Cyanamide*. https://echa.europa.eu/documents/10162/3c41f6a9-2ed9-aaf2-c621-a697d84ef25b

Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). (2020). GESTIS International Limit Values. Accessed January 2020 http://limitvalue.ifa.dguv.de

International Agency for Research on Cancer (IARC), accessed January 2020. https://monographs.iarc.fr/list-of-classifications

National Library of Medicine (NLM) PubChem database accessed February 2020: Compound Summary – *Cyanamide*. https://pubchem.ncbi.nlm.nih.gov/compound/Cyanamide

National Toxicology Program (NTP) Report on Carcinogens (RoC). (14th Edition, 2016). Accessed February 2020. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html

SafeWork Australia. (2019). *Cyanamide – draft evaluation report WES*. https://engage.swa.gov.au/50013/documents/117912

Scientific Committee on Occupational Exposure Limits (SCOEL). (2003). *Recommendation from the Scientific Committee on Occupational Exposure Limits for Cyanamide*. SCOEL/SUM/100_rev. https://circabc.europa.eu/ui/group/a30e5d1c-997c-4cc7-8835-1e4a3205b0b6/library/33a94d31-d1ac-4fa5-b941-4ce2d8ea2e36/details

WorkSafe New Zealand. (2020). Special guide *Workplace Exposure Standards and Biological Exposure Indices* (12th Ed.) November 2020. worksafe.govt.nz/topic-and-industry/work-related-health/monitoring/exposure-standards-and-biological-exposure-indices

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