



# Recommendation from the Scientific Committee on Occupational Exposure Limits for Cyanamide

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## Recommendation from the Scientific Committee on Occupational Exposure Limits for Cyanamide

8 hour TWA	:	1 mg/m <sup>3</sup>
Additional classification	:	Sk

Cyanamide	:	CH <sub>2</sub> N <sub>2</sub>	H <sub>2</sub> N-C≡N
Synonyms	:	amidocyanogen, carbimide, hydrogen cyanamide, carbamonitrile, cyanoamine, N-cyanoamine, cyanogenamide	
EINECS No	:	615-013-00-2	
EEC No	:	206-992-3	
Classification	:	R21-25-36/38-43	
CAS No	:	420-04-2	
MWt	:	42.04	
Conversion factor	:	1 mg/m <sup>3</sup> = 0.58 ppm 1 ppm = 1.72 mg/m <sup>3</sup>	

This summary is based on the criteria documents on cyanamide (DFG 2002) and calcium cyanamide (DFG 1993, 1997) from the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Workplace of the Deutsche Forschungsgemeinschaft. In this documentation a number of unpublished reports sponsored by SKW Trostberg (SKW) are cited which have been made available to the German Commission.



## 1. Occurrence / Use

At room temperature, cyanamide is a crystalline solid but is deliquescent and combustible. It is often stored as a 25 % liquid solution but can, through the evaporation of aqueous solutions to dryness, undergo explosive polymerisation. It is soluble in water (78g/100ml), alcohols, ethers, ketones, but is less soluble in benzene and halogenated hydrocarbons. Decomposition, which begins at 122°C, produces dicyandiamide (via dimerisation), hydrogen cyanide, oxides of nitrogen and carbon monoxide (see SCOEL/INF/581).

Cyanamide is used in chemical syntheses *inter alia* as an intermediate for dicyandiamide in melamine production, as a fumigant, in metal cleaning and refining of ores and the production of synthetic rubber. Cyanamide and its calcium salt has been used as a therapeutic agent for its "Antabuse-like " effect in the treatment of alcoholics. Its effect is to inhibit aldehyde dehydrogenase, leading to an enhanced acetaldehyde level following alcohol consumption (DeMaster *et al.* 1983; Piera *et al.* 1993).

## 2. Health significance

### 2.1. Metabolism and toxicokinetics

Cyanamide can be absorbed via the lung, the digestive tract and the skin in experimental animals and humans. The primary elimination route is urinary excretion. After oral administration, up to 40% of <sup>14</sup>C-radioactivity was eliminated via urine within 48 h in humans, up to 87% within 27 h in dogs and up to 95% within 168 h in rats. The main metabolite in animals and humans is N-acetylcyanamide (Shirota *et al.* 1984). A comparative *in vitro* dermal penetration study in human and rat skin (SKW) indicates considerable absorption of cyanamide (26-80%). In a dermal absorption study in male rats (SKW) the total amount of <sup>14</sup>C-hydrogen cyanamide absorbed ranged from 2 to 11% depending on the dose applied.

### 2.2. Acute toxicity

An LC<sub>50</sub> of >1 000 mg/m<sup>3</sup> was reported in rats following 4 h exposure to cyanamide (SKW). From animal studies, the oral LD<sub>50</sub> has been calculated to be 125 mg/kg bw (Budavari *et al.* 1989). This was confirmed in other studies in rats (SKW), where the LD<sub>50</sub> ranged from 100 to 223 mg/kg.

After dermal application the LD<sub>50</sub> in rabbits was between 742 and 3 200 mg/kg bw (SKW). An LD<sub>50</sub> value of 56 mg/kg bw was reported for intravenous administration (Izmerov 1982).

#### *Local effects*

In a 2-week study in rats (SKW) with exposure for 6 h/day, 5 d/w at 1 484, 2 629 and 7 991 mg/m<sup>3</sup>, no signs of respiratory tract irritation were reported; histopathological investigations of the respiratory tract were not conducted.

Studies on acute dermal irritation performed with 50% cyanamide in aqueous solution on abraded or intact skin for 4 h under occlusive conditions (SKW) show slight to severe erythema and oedema as well as necroses. Under semi-occlusive conditions on intact skin, slight to moderate erythema and slight oedema were observed.

Eye irritation was apparent after application of 0.1 ml 50% cyanamide in aqueous solution in the conjunctival sac of New Zealand White rabbits (SKW), indicated by slight redness, moderate to severe swelling, corneal opacity and slight iritis.



### 2.3. Sensitisation

Cases of skin sensitisation in humans have been reported in several studies, which were confirmed by patch testing with 0.01% to 5% cyanamide in humans. In a study in a calcium cyanamide production unit and associated areas of SKW Trostberg AG, 29 workers showed no signs of skin sensitisation after patch testing with 0.5% cyanamide (Mertschenk *et al.* 1991). Skin reactions that were presumed to reflect allergic reactions to cyanamide, but without detailed information on diagnosis, were observed in humans after contact with cyanamide or its calcium salt. A positive result was documented in a drug lymphocyte stimulation test and a patch test in a 64-year-old male after treatment with cyanamide for alcoholism (see DFG 2002).

Guinea pigs gave a positive result in one maximisation test (induction concentration: intradermally 10% in water or topically 5% in Vaseline; challenge concentration: 1% and 2.5% in Vaseline) (SKW). However, in a Buehler test, 20% cyanamide did not induce sensitisation in guinea pigs (SKW). No evidence has emerged to suggest that cyanamide has respiratory sensitisation potential.

### 2.4. Toxicity after repeated exposure

#### Inhalation

5-8 rats were exposed to cyanamide aerosol concentrations of 1 484, 2 629 or 7 991 mg/m<sup>3</sup> for 6h/day, 5d/w for 2 weeks (SKW). No mortality and no clinical signs occurred. Body weight decreased in relation to dose and time, whereas food consumption was only slightly reduced in females. Relative organ weights (brain, kidney, gonads, liver and heart) were elevated at 1 484 mg/m<sup>3</sup> but without concomitant histopathological findings at this dose level. At 7 991 mg/m<sup>3</sup> microscopic examination revealed microcavitation in the brain, cloudy swelling in the liver, minute oedematous areas in the myocardium and bronchiectasis. The reliability of the study is limited because there are no histopathological examinations of the upper respiratory tract and no information about particle size and distribution.

#### Oral application

There are several subchronic and chronic studies in dogs, rats and mice, with dogs appearing to be the most sensitive species (see DFG 2002). In a study with beagles treated with 50% cyanamide in water over 52 weeks (SKW), a NOAEL of 0.2 mg/kg bw/day per day was determined. This study was performed according to GLP. Groups of four dogs per sex were treated with 0, 0.1, 0.5 or 2.5 mg cyanamide/kg bw/day for 2 weeks. Thereafter, the dose levels were increased by a factor of 2 for the remaining 50 weeks, resulting in dose levels of 0.2, 1 or 5 mg cyanamide/kg bw/day. There was no mortality during the course of the study. The animals in the high-dose group (5 mg/kg bw/day) showed signs of tremor, increased saliva (also seen in one female dog in the intermediate dose group) and reduction in body weight gain. In addition, haematological and clinico-chemical analysis revealed a decrease of mean cell haemoglobin concentration (male and female), albumin (male and female), thyroxine (male and female), aspartate/alanineaminotransferase activity (male and female), neutrophils (male), haemoglobin (female), serum urea (female), creatinine (female), glucose (female), calcium (female) and enhanced values for monocytes (male and female), lymphocytes (male and female), globulin (male and female) and inorganic phosphate (male). At 1 mg/kg bw/day and above, a reduction of mean cell volume (male and female), thrombocytes (male), mean cell haemoglobin (female) and enhanced values for cholesterol (male and female) and leucocytes (male) were observed. The histopathological examination revealed enhanced haematopoiesis in spleen (male), pale areas on spleen (female), pigmentation of Kupffer's cells (male and female), microstones in the gallbladder (male and female), atrophy of thymus (male), increased relative thyroid



weight and reduced immature sperm count, chronic inflammation of testes at 5 mg/kg bw/day.

In humans, a few chronic alcoholic subjects treated daily with 20 mg (approx. 0.3 mg/kg bw/day) cyanamide showed a mild anti-alcoholic reaction of transient parasympathetic overactivity. At higher doses elevated levels of liver enzymes and hepatocellular ground glass inclusions have been detected. There are several reports on the therapeutic use of cyanamide in alcoholics (Villegas 1984, Vázquez *et al.* 1983, Vázquez and Cervera 1980, Bruguera *et al.* 1986, Thomson and Reinicke 1981, Yokoyama *et al.* 1995). The therapeutic principle is to cause aversion to alcohol consumption by increased acetaldehyde levels due to inhibition of acetaldehyde dehydrogenase activity. Symptoms are vasodilation characterised by facial flushing, headaches, nausea, hypotension and vertigo (Hathaway *et al.*, 1991). In these reports daily doses between 20 and 180 mg (0.3-2.5 mg/kg) have been given. Evaluation of the hepatic effects observed are complicated by the alcohol consumption. However, Villegas (1984), who treated 33 alcoholics with daily doses between 120 and 180 mg for 1 year, reported an improved hepatic function and explained this with the reduced alcohol consumption. The investigation of Yokoyama *et al.* (1995) on 29 alcoholics treated with cyanamide and drinking alcohol during non-treatment intervals revealed hepatocellular ground glass inclusions, which persisted in 4 alcoholics for 1 to 4 years after cyanamide treatment. Their conclusion was that cyanamide treatment resulted in a progression of the alcohol-induced hepatic disorder. Overall, long-term treatment with daily doses of 0.3-2.5 mg/kg demonstrated an anti-alcoholic reaction in a few subjects and may exert hepatotoxic effects in alcoholics. It is not clear whether this is due to elevated acetaldehyde levels or to cyanamide and/or its metabolites (Mukasa *et al.* 1964; Moreno *et al.* 1984; Yokoyama *et al.* 1995). However, animal studies without concomitant alcohol treatment demonstrated histopathological ground glass hepatocytes and altered serum liver enzyme levels after intraperitoneal and oral cyanamide administration (Válerdiz and Vázquez 1989; Iodate and Vázquez 1992; Guillen and Vázquez 1984). This suggests that cyanamide and/or its metabolites can produce some hepatotoxicity, both in experimental animals and in humans.

Studies in rats have modelled the levels of inhibition of aldehyde dehydrogenase activity and the concomitant increase in acetaldehyde produced by cyanamide, in relation to its use in alcoholism treatment (DeMaster *et al.* 1983; Piera *et al.* 1993).

In a very limited study on endocrine functions in 21 workers engaged in calcium cyanamide production, there was no statistically significant difference in thyroxine, triiodothyronine, thyroglobulin, thyrotropin, testosterone, FSH and LH levels compared with 9 controls (Mertschenk *et al.* 1993). No signs of toxicity were documented after occupational exposure of humans to the fertiliser "Kalkstickstoff" (60% calcium cyanamide, 15% calcium oxide, 10% carbon and calcium salts, silicates, aluminium-, iron- and magnesium oxides; Schiele *et al.* 1981), whereas in some cases of farmers exposed to an unknown concentration of this fertiliser in the fields, with known or questionable alcohol consumption before or after work, mortality and vegetative symptoms were seen (DFG 1993). Owing to lack of exposure concentrations, mixed exposure and methodological limitations, the studies are not useful for this evaluation.

## 2.5. Reproductive toxicity

A two-generation reproduction/fertility study in rats was performed at dose levels of 0, 2, 7 and 25 mg cyanamide/kg bw/day/sex. Exposure started 70 days prior to mating for males and 15 days prior to mating for females. At the highest dose, females had lower body weights and decreased numbers of living neonates, implantations and corpora lutea. Males showed bilateral testicular atrophy and reduced fertility at the highest dose. The



effect seen on the fertility rate has been interpreted by the authors as being related to cyanamide effects in males. No developmental effects were seen in the F<sub>1</sub> generation; however, the number of F<sub>1</sub> pregnant dams decreased from 20 of the controls to 6 at 25 mg/kg bw/day. The NOAEL in the study was 7 mg/kg bw/day; although a decrease in relative prostate weight was observed at this dose level, this was the only finding and, in itself, was judged not to be toxicologically significant (Valles *et al.* 1987).

In a developmental toxicity study (SKW), rats were treated with dose levels of 0, 5, 15 and 45 mg cyanamide/kg bw/day from days 6 to 15 of gestation. Maternal body weight and food consumption were reduced significantly in the two high-dose groups. Developmental toxicity (reduced foetal body weights, diaphragmatic hernia) was seen at 45 mg/kg bw. Developmental effects were not evident at dose levels of 5 or 15 mg/kg bw/day, and therefore the no-embryo/foetotoxic-effect level is 15 mg cyanamide/kg bw/day.

In another developmental toxicity study (SKW), New Zealand White rabbits received dose levels of 2, 5.9 or 17.6 mg cyanamide/kg bw/day from days 6 to 19 of gestation. In the high-dose group a moderate maternal body weight loss was observed. Developmental effects occurred at 5.9 mg/kg bw/day (minor eye anomalies) and above (increased number of early resorptions and dead foetuses, lower mean foetal body weights, relatively high number of small foetuses, increased incidence of several minor anomalies). The NOAEL for maternal toxicity was therefore 5.9 mg cyanamide/kg bw/day and the no-embryo/foetotoxic-effect level was 2 mg cyanamide/kg bw/day.

## 2.6. Genotoxicity

Mutagenicity has been investigated in *Salmonella typhimurium* (TA98, TA100, TA153J, TA1537 and TA1538) and *Escherichia coli*. There was no increase in mutagenic activity with or without metabolic activation (DFG 2002). There was no increase in DNA strand breaks in rat hepatocytes following treatment with cyanamide (Sina *et al.* 1983), nor was it clastogenic in the micronucleus test in mice (Menargues *et al.* 1984).

## 2.7. Carcinogenicity

In an NCI cancer bioassay calcium cyanamide (which readily decomposes to cyanamide) was administered in the diet to F344 rats (0, 5, 10 mg/g bw and day males, 0, 5, 20 mg/kg bw and day, females) and to B6C3F1 mice (0, 75, 300mg/g bw and day) for 100 weeks. Increased incidences of hemangiosarcomas in male mice [control 1/20 (5%), low dose 2/50 (4%), high dose 10/50 (20%), historical control 13/323 (4%)] and of lymphomas or leukaemias in female mice [control 1/20 (5%), low dose 11/46 (24%), high dose 18/50 (36%), historical control 67/324 (21%)] were observed. As the incidences of hemangiosarcomas in male mice or of lymphoma or leukaemias in female mice could clearly be related to the administration of the test chemical, the authors conclude that, under the conditions of this bioassay, the test substance was not carcinogenic for F344 rats or B6C3F1 mice. (National Cancer Institute 1979).

In a carcinogenicity study (SKW), 60 male and female CD-1 mice per group received cyanamide in drinking water at concentrations of 0, 70, 200 or 600 ppm for up to 104 weeks. Intake of the substance was calculated for the low dose as 8.4-12.9 and 11.0-16.4 mg/kg bw/day, for the intermediate dose as 24.3-34.7 and 26.8-43.5 mg/kg bw/day and for the high dose as 59.1-92.2 and 77.9-124.2 mg/kg bw/day for males and females, respectively. In female animals there was a slight excess of morbidity and mortality in the intermediate- and high-dose groups compared to the control group, which was statistically significant in the high-dose group. Body weight gain was reduced for the first 6 weeks in all treated groups of males and in the intermediate- and high-dose groups of females. In female animals, a statistically significant trend for the increase of granulosa-



theca cell tumour incidence was observed: 3/60 (control), 1/60 (low dose), 6/60 (intermediate dose), 8/58 (high dose); this finding needs further clarification.

In a study examining cancer incidence and mortality amongst 790 workers engaged in calcium carbide production, no increase in cancer was seen amongst a sub-set of 117 workers who had worked in cyanamide/dicyandiamide production for at least 18 months between 1953 and 1970. No exposure data are given (Kjuus *et al.* 1986).

## Recommendations

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<sup>3</sup> for 8 hours per day, assuming 100% retention and absorption of inhaled material, a breathing volume of 10 m<sup>3</sup> 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.





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