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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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2-Chloro-acrylonitrile

No. 38

CAS No. 920-37-6

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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2-Chloroacrylonitrile

1 Summary and assessment

2-Chloroacrylonitrile, under appropriate conditions of exposure, is absorbed by the body both via the skin and the gastrointestinal tract as well as via the respiratory tract.

In acute exposure, 2-chloroacrylonitrile is toxic after oral and dermal administration. The oral LD_{50} in the rat and the mouse is between 25 and 230 mg/kg body weight and about 200 mg/kg body weight following dermal application in rats. Upon inhalation 2-chloroacrylonitrile is very toxic (with an LC_{50} of approx. 100 mg/m³ in the rat and the mouse). The signs of toxicity are mostly unspecific (convulsions, dyspnoea, rough coat). Frequently dilation of the heart and congestion of the lung are observed.

2-Chloroacrylonitrile is corrosive to the skin and the mucous membranes. Direct contact of the eye with the undiluted substance leads to the destruction of the eye.

Appropriate studies for the evaluation of the systemic effects of 2-chloroacrylonitrile following repeated or chronic administration are lacking. From one 4-month oral study, which has been reported only as a short summary, there is evidence of impairment of liver and kidney function.

Some evidence of possible nephrotoxicity is also furnished by the findings of an in vitro study in primary renal tubular cells, showing that the conjugate of 2-chloroacrylonitrile with glutathione markedly inhibits the uptake of p-aminohippurate into the cells.

In the Salmonella/microsome assay with the *Salmonella typhimurium* strain TA 100, three independent studies report that 2-chloroacrylonitrile causes a concentration-dependent increase in the numbers of revertants of up to a maximum of twice the control counts, thus exhibiting weak mutagenicity in this test system. The SOS-chromotest in *Escherichia coli* PQ 37 has not shown any evidence of DNA-damaging effects of the substance. No further tests have been conducted regarding the genotoxicity or carcinogenicity of 2-chloroacrylonitrile. On account of its close structural analogy with acrylonitrile, a confirmed carcinogen in experimental animals, it is urgently sus-

pected that 2-chloroacrylonitrile also possesses carcinogenic properties. Final evaluation of the substance is not possible due to the lack of relevant studies.

One study investigating reproductive toxicity in rats shows that inhalation of 2-chloroacrylonitrile for 6 hours/day from days 6 to 20 of gestation at concentration levels causing maternal toxicity (3.63, 21.78 and 43.54 mg/m³) does not produce foetotoxic or teratogenic effects. All parameters, except maternal body weight gain at the highest and mid concentrations, corresponded to the controls.

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has assigned 2-chloroacrylonitrile to category 3 of carcinogenic substances (i.e. "substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data"). On the other hand, the substance has not been legally classified in the TRGS 905.

2 Name of substance

2.1	Usual name	2-Chloroacrylonitrile
2.2	IUPAC name	2-Chloroacrylonitrile
2.3	CAS No.	920-37-6
2.4	EINECS No.	213-055-2

3 Synonyms, common and trade names

CACN
2-Chloracrylnitril
Chloroacrylonitrile
α-Chloroacrylonitrile
2-Chloro-2-propenenitrile

4 Structural and molecular formulae

4.1	Structural formula		
4.2	Molecular formula	C_3H_2ClN	

5 Physical and chemical properties

5.1	Molecular mass, g/mol	87.5	
5.2	Melting point, °C	–65	(Bayer, 1998 a; Lide and Frederikse, 1996; Penzel, 1992)
5.3	Boiling point, °C	88–89 88.5 89	(Bayer, 1998 a) (Lide and Frederikse, 1996) (Penzel, 1992)
5.4	Vapour pressure, hPa	66.8 (at 20 °C) 85.4 (at 25 °C) 257 (at 50 °C)	 (Bayer, 1998 a)
5.5	Density, g/cm³	1.085 (at 25 °C) 1.088 (at 20 °C) 1.096 (at 25 °C)	(Penzel, 1992) (Bayer, 1998 a) (Lide and Frederikse, 1996)
5.6	Solubility in water	Ca. 10 g/l (at 25 °C)	(Bayer, 1998 a; Penzel, 1992)
5.7	Solubility in organic solvents	Completely miscible with polar solvents, partly miscible with nonpolar solvents	(Münzing, 1971)
5.8	Solubility in fat	No information available	
5.9	pH value	Not applicable	(Bayer, 1998 a)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 3.63 mg/m³ 1 mg/m³ ≙ 0.275 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

As a monomer for the production of plastics and in the synthesis of dyestuffs and pharmaceuticals (Münzing, 1971). Intermediate in the synthesis of agricultural chemicals and photochemical products (Bayer, 1998 b).

7 Experimental results

7.1 Toxicokinetics and metabolism

No studies of the toxicokinetics and metabolism of 2-chloroacrylonitrile are available.

From the available findings from animal experiments it can be concluded that particularly with respect to its acute toxicity 2-chloroacrylonitrile is rapidly absorbed via both the skin and the gastrointestinal tract as well as the respiratory tract under the appropriate conditions of exposure. In a brief summary it is described that 2/3 of the rats died after their tails had been submerged in 2-chloroacrylonitrile for 4 hours. The tails exhibited necrotic changes (no further data; Gizhlaryan and Khechumov, 1983).

7.2 Acute and subacute toxicity

The acute toxicity data are summarised in Table 1 below. They demonstrate that 2-chloroacrylonitrile is highly toxic in all routes of administration used. On ingestion or contact with the skin the substance is definitely toxic and it is very toxic upon inhalation. At high doses, death occurs rapidly.

Beginning of Table 1

Table 1. Acute toxicity of 2-chloroacrylonitrile					
Species, strain, sex*	Route	Dose (mg/kg body weight or mg/m³)	Effects	Observation period	Reference
Rat, Sprague-Dawley, male	oral	78	LD_{50}; dyspnoea, agonal convulsions, sedation, ataxia, no specific pathological findings	14 days	LPT, 1978

Table 1. Acute toxicity of 2-chloroacrylonitrile					
Species, strain, sex*	Route	Dose (mg/kg body weight or mg/m³)	Effects	Observation period	Reference
Rat	oral	> 32 < 38	LD_{50}; unspecific signs of toxicity; dilation of the heart and congestive hyperaemia, acute emphysema of the lung, corrosive gastritis, peripherolobular markings of the liver lobules	14 days	BASF, 1978
Rat	oral	230	LD_{50}; no further data	no data	Gizhlaryan and Khechumov, 1983
Rat	oral	25–50	LD_{50}; restlessness, vasodilatation, convulsions, slight tremor, rough coat	14 days	Eastman Kodak, 1971
Mouse	oral	128	LD_{50}; no further data	no data	Gizhlaryan and Khechumov, 1983
Mouse	oral	25–50	LD_{50}; weak ataxia and rough coat	14 days	Eastman Kodak, 1971
Rat	dermal	ca. 200	LD_{50}; apathy; congestive hyperaemia and acute dilation of the heart, congestion of the lung	14 days	BASF, 1978
Rabbit	dermal	< 218 (< 200 µl)	LD_{50}; myosis, reddened iris, salivation, dyspnoea, convulsions and tremor; congestive hyperaemia and acute dilation of the heart, congestion of the lung; no mortality data	14 days	BASF, 1978
Guinea pig	dermal	109–1088	LD_{50}; severe skin damage at the site of application	14 days	Eastman Kodak, 1971
Rat	inhalative	vapour-enriched atmosphere at 20 °C	inhalation hazard test; all 12 animals died within 3 minutes; convulsions, mucous membrane irritation, dilation of the heart with congestive hyperaemia, congestion of the lung, markings of the liver lobules	–	BASF, 1978

Table 1. Acute toxicity of 2-chloroacrylonitrile					
Species, strain, sex*	Route	Dose (mg/kg body weight or mg/m³)	Effects	Observation period	Reference
Rat, male and female, Wistar, Hsd Win:WU	inhalative	102	LC_{50} after a 4-hour exposure; dyspnoea, cyanosis, limited mobility, rough coat, piloerrection; congestion of the lung	14 days	Bayer, 1995
Mouse	inhalative	105	LC_{50} after a 2-hour exposure; no further data	no data	Gizhlaryan and Khechumov, 1983
Rat	intraperitoneal	10–25	LD_{50}; convulsions, vasodilatation, dyspnoea, cyanosis, rough coat	14 days	Eastman Kodak, 1971
Mouse	intraperitoneal	14	LD_{50}; unspecific signs of toxicity	14 days	BASF, 1978
Mouse	intraperitoneal	10	LD_{50}; tremor, rough coat	14 days	Eastman Kodak, 1971
* where indicated					

End of Table 1

7.3 Skin and mucous membrane effects

2-Chloroacrylonitrile caused severe reddening, oedema and necrosis in rabbits following 3-minute, 1-hour and 4-hour applications to the skin. The local changes appeared even before the end of the application period in the longer applications, and within 24 hours in the case of the 3-minute application, none of the changes being reversible within 8 days (BASF, 1978). The substance thus exhibited a corrosive effect on the skin in this test.

Application of 2-chloroacrylonitrile to the dorsal skin of rabbits in a further study led to the formation of badly healing (observation period of 40 days) running abscesses (no further data; Gizhlaryan and Khechumov, 1983).

In a study in which guinea pigs were exposed to doses in the lethal range (0.1 to 5.0 ml/kg body weight), application of undiluted 2-chloroacrylonitrile led to severe oedema and necrosis within the first 24 hours, extensive escar formation after one week and heavy scarring after 2 weeks (Eastman Kodak, 1971). The substance thus also exhibited a corrosive effect on the skin of guinea pigs.

Instillation of 50 mg of undiluted 2-chloroacrylonitrile into the conjunctival sac of the rabbit eye caused very severe oedema as early as one hour after application, followed in addition by very severe erythema of the nictitating membranes and sanguinous discharge after 24 hours. After 8 days the oedema, gross purulent discharge and white mucous membranes continued to persist (BASF, 1978). The substance was thus corrosive to the rabbit eye.

In a further study it was observed that instillation of 0.1 ml of undiluted 2-chloroacrylonitrile into the conjunctival sac of the rabbit eye produced severe damage to the connective tissue and the cornea to the extent that the animal went blind (no further data; Gizhlaryan and Khechumov, 1983). Again, the substance was thus corrosive to the rabbit eye.

An earlier study in the rabbit eye also confirmed the corrosive effect of 2-chloroacrylonitrile. Just one drop of the undiluted substance caused severe oedema on most parts of the eye as soon as one hour after application. The cornea was not visible. After 48 hours gross purulent discharge and hard lids were observed and the eye was sunken in the socket so that the animal had to be killed (Eastman Kodak, 1971).

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

With respect to the subchronic toxicity of 2-chloroacrylonitrile no more data are available than those presented in a very brief summary. According to this source, a 4-month exposure to $^{1}/_{10}$ of the LD_{50} (23 mg/kg body weight) is reported to have led to impairment of hepatic function in rats. The biosynthesis of hippuric acid, the results of the bromosulphthalein test and the galactose tolerance tests as well as the serum transaminase levels were reported to have been negatively affected. Moreover, there was mention of impaired renal function (alterations with respect to diuresis, density of the urine and urinary chloride, protein and creatinine levels). In addition, adrenal function (Thorn's test) and the blood counts were altered, according to the report (no further data; Gizhlaryan and Khechumov, 1983). In view of

this insufficient documentation, evaluation of the subchronic toxicity of 2-chloroacrylonitrile is possible only to a limited extent.

7.6 Genotoxicity

7.6.1 In vitro

2-Chloroacrylonitrile was described to possess a weak mutagenic effect in a Salmonella/microsome assay. The test used the Salmonella typhimurium strain TA 100 without metabolic activation. The number of revertants was more than double the control counts (no further data; Rosen et al., 1980).

In a further Salmonella/microsome assay, strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were used. Assays were performed without metabolic activation as well as in the presence of S9 mix prepared from livers of rats treated with Aroclor 1254. 2-Chloroacrylonitrile was tested at the following concentration levels, given in µg/plate: 1.58, 5, 15.8, 50, 158, 500, 1580 and 5000. At the two highest concentration levels, bacteriotoxic effects were observed. In strain TA 100 as well as in the presence of S9 mix, a concentration-dependent mutagenic effect was observed at 2-chloroacrylonitrile concentrations of 500 µg/plate, which led to a 2-fold increase in the number of revertant colonies. In the absence of S9 mix and in the assays in which other bacterial strains were used 2-chloroacrylonitrile did not exhibit mutagenic activity. The authors considered the substance to be mutagenic (RCC, 1983).

In a Salmonella/microsome assay which was carried out with strain TA 100 in the absence of metabolic activation and in the presence of S9 mix from livers of rats treated with Aroclor, a mutagenic effect was found which the authors considered questionable. In the incubation test, concentration levels were used ranging from 0.125 to 3.131 nM of 2-chloroacrylonitrile (purity > 99%). The number of revertants increased in a dose-dependent manner up to a 2-chloroacrylonitrile concentration of 1.566 nM, reaching the 1.5-fold number in the absence of S9 mix and the nearly 2-fold number in the presence of S9 mix. Taking into account that the test was carried out as a preincubation test, the authors point out the possibility that in view of the high volatility of 2-chloroacrylonitrile the concentration of the substance in the incubation medium may have dropped considerably (Eder et al., 1994).

In a SOS-chromotest in Escherichia coli PQ 37 with concentration levels of 2-chloroacrylonitrile (> 99%; measured as the increase in galactosidase activity) ranging from 0.6 to 155 nM, 2-chloroacrylonitrile was not found to have any DNA-damaging effect (Eder et al., 1994).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

Pregnant Sprague-Dawley rats were subjected to inhalative (whole-body) exposure to 2-chloroacrylonitrile in groups of 20 to 23 animals from day 6 to day 20 of gestation for 6 hours per day. The concentration levels of 2-chloroacrylonitrile (99% purity) used were 0 (controls), 1, 6 and 12 ppm (0, 3.63, 21.78 and 43.56 mg/m³, respectively). On day 21 of gestation all dams were killed and subjected to Caesarean section. No dam had died during gestation. Body weight gain was depressed in a concentration-dependent manner at the 6 and 12 ppm exposure levels. 2-Chloroacrylonitrile did not cause any changes in the numbers of implantations, the live foetuses and resorptions, and it did not have any effect on the foetal sex ratio or foetal weights as compared with the controls. Abnormal skeletal variants and malformations of the organs were not observed beyond the spontaneous rates seen in the controls (Saillenfait et al., 1993). The *no observed adverse effect level* (NOAEL) for the foetuses and the dams was thus 43.56 mg/m³ and 3.63 mg/m³, respectively.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

In an in vitro study in primary renal tubular cells which were isolated from the kidneys of male Fischer-344 rats, the N-acetyl-1,5,2-cyanoethylcysteine formed as the conjugate of 2-chloroacrylonitrile with glutathione inhibited the uptake of p-aminohippurate in a concentration-dependent manner. The cells were incubated for 15 minutes with the conjugate at concentration levels of 0.1, 0.2, 0.5 and 1.0 mM whereupon p-aminohippurate (72 µM) was added and the uptake of the substance by the cells was determined by analysis after an additional 5 minutes. Starting at levels of 0.2 mM, the glutathione conjugate of 2-chloroacrylonitrile inhibited uptake in a concentration-dependent manner, producing up to 50% inhibition at 1.0 mM. The authors presume that conjugation of 2-chloroacrylonitrile also takes place in vivo and they interpret their findings in terms of a nephrotoxic effect of 2-chloroacrylonitrile (Craan and Malick, 1989).

8 Experience in humans

No information available.

9 Classifications and threshold limit values

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) of the Deutsche Forschungsgemeinschaft has assigned 2-chloroacrylonitrile to category 3 of carcinogenic substances (i.e. “substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data”; DFG, 1994, 1999). On the other hand, the substance has not been legally classified in the TRGS 905 (TRGS 905, 2000).

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