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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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3-Chloro-propanoic acid chloride

No. 162

CAS No. 625-36-5

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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3-Chloropropanoic acid chloride

In addition to 3-chloropropanoic acid chloride, Toxicological Evaluations are available on its structural homologues, 4-chlorobutanoic acid chloride (online) and chloroacetyl chloride (cf. volume 12), and these evaluations may be consulted for comparison.

In the presence of water, 3-chloropropanoic acid chloride is completely hydrolysed to 3-chloropropanoic acid and hydrochloric acid within 5 minutes. At least part of the compound's toxicological effect is likely to be attributable to these products of hydrolysis.

1 Summary and Assessment

According to the studies available, 3-chloropropanoic acid chloride is acutely harmful on oral administration (LD_{50} rat oral approx. 1200 mg/kg body weight). In the inhalation hazard test, all 6 rats died after only 3 minutes of exposure. In the Alarie (sensory irritation) test, the RD_{50} (i. e. the concentration at which the rate of respiration is reduced by 50%) was 73 mg/m³.

3-Chloropropanoic acid chloride is severely corrosive to the skin, the eye and the respiratory tract even after very short exposure.

In the Salmonella/microsome assay, 3-chloropropanoic acid chloride is found to be mutagenic both with and without metabolic activation. Without giving any further details, it has been reported that 3-chloropropanoic acid chloride has tested positive in the SOS chromotest in *Escherichia coli* in the absence of an exogenous metabolic activation system. In human leukocytes, the substance causes no chromosome aberrations in the presence and absence of metabolic activation. No conclusive assessment of the substance's genotoxic potential is possible on the basis of these results.

2 Name of substance

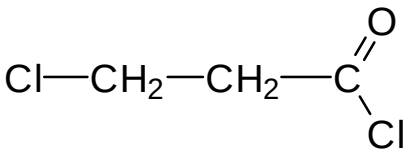
2.1	Usual name	3-Chloropropanoic acid chloride
2.2	IUPAC name	3-Chloropropanoic acid chloride
2.3	CAS No.	625-36-5
2.4	EINECS No.	210-890-4

3 Synonyms, common and trade names

3-Chloropropanoyl chloride
3-Chloropropionyl chloride
3-Chlorpropanoylchlorid
3-Chlorpropionsäurechlorid
3-Chlorpropionylchlorid
β-Chloropropionyl chloride
β-Chlorpropionsäurechlorid
β-Chlorpropionylchlorid

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_3H_4Cl_2O$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	126.97	
5.2	Melting point, °C	ca. –32	(BASF, 1995)
5.3	Boiling point, °C	143–145	(Riedel-de Haën, 1995)
		144	(Samel et al., 1993; Lide and Frederikse, 1996)
		45–55 (at 27 hPa)	(BASF, 1987)

5.4	Vapour pressure, hPa	10 (at 20 C°)	(BASF, 1995)
5.5	Density, g/cm³	1.3307 (at 13 °C)	(Lide and Frederikse, 1996)
		1.33 (at 13 °C)	(BASF, 1995)
		1.33 (at 20 °C)	(Riedel-de Haën, 1995)
5.6	Solubility in water	Decomposes completely within 5 minutes to form 3-chloropropanoic acid and hydrochloric acid	(BASF, 1997)
		Low	(Lide and Frederikse, 1996)
5.7	Solubility in organic solvents	Dissolves well in ethanol, diethyl ether, chloroform	(Lide and Frederikse, 1996)
		Miscible with nearly all common aprotic organic solvents	(BASF, 1981)
5.8	Solubility in fat	No information available	
5.9	pH value	< 7 due to hydrolysis	(BASF, 1987)
		Acidic	(BASF, 1995)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 5.18 mg/m³ 1 mg/m³ ≙ 0.19 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

Intermediate used in the chemical industry for the manufacture of dyestuff precursors, textile auxiliaries, pharmaceuticals as well as crop protection and pest control agents (BASF, 1981, 1995).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

The oral toxicity of 3-chloropropanoic acid chloride, formulated as an aqueous suspension with tragacanth and as a solution in olive oil, was determined in male and female Sprague-Dawley rats. The observation pe-

riods were 7 and 14 days, respectively. The resulting LD_{50} values were nearly identical; approx. 1200 mg/kg body weight and of > 1000 but < 1500 mg/kg body weight were found for the aqueous suspension and the solution in olive oil, respectively. The animals died within 24 hours. The signs of toxicity were consequences of the corrosive effects of the product, as were the main necropsy findings. (BASF, 1968, 1980).

In the inhalation hazard test, exposure to atmosphere enriched with 3-chloropropanoic acid chloride at 20 °C was lethal to all 6 rats used in the study after a period of only 3 minutes. At the start of exposure, attempts to escape were observed, followed by dyspnoea to the extent of gasping as well as severe irritation of the mucous membranes. After exposure, the animals continued to display dyspnoea accompanied by wheezing until they died. Necropsy revealed severe oedema of the lung (BASF, 1968; EPA, 1992).

In a further study, tests were carried out in accordance with the requirements of the U.S. Department of Transportation (DOT). Twelve rats were exposed for one hour to a nominal concentration of 200 ppm. Death resulted in 9 out of 12 animals (BASF, 1968).

The sensory irritation potential of 3-chloropropanoic acid chloride (> 96% pure) was studied in groups of 4 Swiss CD1 mice in accordance with OECD guideline No. 403. The animals were exposed once to analytically determined concentrations of, on average, 49, 70, 136 and 160 mg/m³ for a period of 30 minutes. Respiration rate was recorded by plethysmography 10 minutes before, during and at least 10 minutes after exposure. In all groups, slight body weight loss was observed on the day after exposure. During exposure itself, breathing frequency was observed to decrease with time. In the mice of the two top concentration groups post-inspiratory apnoea was seen, which also occasionally occurred in the animals exposed to the lower levels. Macroscopic examination carried out 7 days after exposure revealed grey discoloured lungs in one mouse from each of the three highest level groups. The concentration leading to a 50-percent decrease in breathing rate (RD_{50}) was calculated according to two different methods yielding values of 72 and 73 mg/m³ (TNO, 1997).

Following a single intraperitoneal injection and a 7-day observation period, 3-chloropropanoic acid chloride was found to have an LD_{50} of approx. 40 mg/kg body weight in mice (no further details; BASF, 1968).

7.3 Skin and mucous membrane effects

To study the skin irritancy of 3-chloropropanoic acid chloride, the undiluted substance was applied to the shorn dorsal skin of white rabbits for 1 minute, 5 and 15 minutes, and 20 hours. Following the 1-minute exposure, severe reddening and slight desquamation were seen after 24 hours and 8 days, respectively. On 5-minute exposure, slight necrosis with reddening and oedema were observed after 24 hours. After 8 days, necrosis was very severe. The 15-minute application resulted in severe necrosis with reddening of the peripheral areas, and oedema (finding after 24 hours and 8 days). On 20-hour exposure, very severe necrosis developed, accompanied by reddening of the surrounding skin and severe oedema. In addition, purulent inflammation developed by day 8 following exposure. A 20-hour application to the rabbit ear resulted in severe necrosis after 24 hours and loss of the ear (BASF, 1968).

In the rabbit eye, one drop of undiluted 3-chloropropanoic acid chloride was corrosive to the mucous membranes and the cornea. In addition, purulent inflammation had developed by day 8 (BASF, 1968).

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

3-Chloropropanoic acid chloride (96.9% and 99.7% pure) was tested for mutagenicity in the Salmonella/microsome assay (standard-plate incorporation test) with and without metabolic activation (S-9 mix from Aroclor 1254-induced rat liver) using the *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 (in accordance with OECD guideline No. 471). The concentrations employed in the experiments with metabolic

activation were 10, 100, 333.3, 1000 and 5000 µg/plate, while in the absence of metabolic activation concentrations of 10, 100, 333.3, 666.6, 1000, 2500 and 5000 µg/plate were used. The highest concentration was found to be bacteriotoxic. Both in the presence and absence of metabolic activation, strains TA 1535, TA 1537 and TA 100 displayed concentration-dependent increases in revertant counts, which in TA 1535 was seen even at the lowest concentration (10 µg/plate). In the other two strains, the lowest effective dose was 100 µg/plate. 3-Chloropropanoic acid chloride therefore proved to be mutagenic in this test system (CCR, 1991).

3-Chloropropanoic acid, the hydrolysis product of 3-chloropropanoic acid chloride, was also found to be mutagenic at concentrations ranging from 50 to 1000 µg/plate in the Salmonella/microsome assay with the *Salmonella typhimurium* strains TA 100 and TA 1535 in the absence of metabolic activation (no further details; Simmon, 1978; Szegedi, 1989).

Both 3-chloropropanoic acid chloride and its hydrolysis product, 3-chloropropanoic acid, were tested for genotoxicity in the SOS chromotest using *Escherichia coli* without metabolic activation and gave a positive response in that test system (no further details; Szegedi, 1989).

The chromosome-damaging potential of 3-chloropropanoic acid chloride (purity according to the certificate of analysis: 100.08%) was studied in vitro in human lymphocytes, with and without metabolic activation (S-9 mix from Aroclor 1254-induced rat liver), in accordance with OECD guideline No. 473. In a preliminary cytotoxicity study, 3-chloropropanoic acid chloride was investigated at concentrations ranging from 40 to 1000 µg/ml. The concentrations for the main study were chosen with respect to the quality of the metaphases rather than the mitotic index, as would have been required by the guideline. This procedure was chosen since the required reduction in mitotic index (by approx. 50%) occurred at concentrations that interfered with chromosomal structure („fuzzy chromosomes“) to the extent that evaluation was not possible (no further details). Therefore concentrations of 5, 10 and 20 µg/ml were used in the absence of metabolic activation, whereas in the presence of metabolic activation 60, 125 and 250 µg/ml were tested. Positive controls were treated with mitomycin C (0.1 µg/ml) and cyclophosphamide (5 µg/ml). The incubation periods were 24 hours (without S-9 mix), or 3 hours, followed by an additional 21 hours without the test substance (with S-9 mix). Following addition of colcemid, 100 metaphases

per culture were analysed for chromosome aberrations. 3-Chloropropanoic acid chloride did not affect the number aberrant metaphases, including and excluding gaps, either with or without metabolic activation, and therefore did not have a clastogenic potential (BASF, 1992).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

The induction of pulmonary adenomas by 3-chloropropanoic acid, the hydrolysis product of 3-chloropropanoic acid chloride, was investigated in a screening study in strain A mice. Groups of 20 mice (10 males and 10 females, 6 to 8 weeks old) received intraperitoneal injections of 3-chloropropanoic acid in physiological saline solution 3 times per week for a period of 8 weeks at doses of 0 (controls), 0.14 and 0.28 mmol/kg body weight (equivalent to 0, 17.8 and 35.6 mg/kg body weight), and 12 times within an 8-week period at a dose of 0.56 mmol/kg body weight (equivalent to 71.1 mg/kg body weight; i. e. the maximum tolerated dose as established in the preliminary study) (no further details). The observation period was 16 weeks. One animal of the lowest dose group and 10 others of the highest dose group died during the study. At the end of the observation period, the incidence of pulmonary adenomas was significantly increased in the group treated with 0.56 mmol/kg as compared with the control group receiving physiological saline solution (0.90 tumours/mouse, control group 0.10 tumours/mouse; Theiss et al., 1979). The indicative value of this method is limited due to the fact that study duration is too short, the number of animals per dose group is too small and the incidence of spontaneous lung tumours is high in strain A mice.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

No information available.

8 Experience in humans

No information available.

9 Classifications and threshold limit values

No information available.

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