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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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4-Chloro-butanoic acid chloride

No. 163

CAS No. 4635-59-0

BG Chemie
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4-Chlorobutanoic acid chloride

Apart from the present evaluation of 4-chlorobutanoic acid chloride, TOXICOLOGICAL EVALUATIONS of 3-chloropropanoic acid chloride (online) and chloroacetyl chloride (volume 12) have been published and both may be consulted for comparison.

4-Chlorobutanoic acid chloride is hydrolysed to 4-chlorobutanoic acid and hydrochloric acid in the presence of water, with most of the reaction taking place within the first 5 minutes and complete decomposition being reached after 30 minutes. At least part of the compound's toxicological effect is likely to be attributable to these products of hydrolysis.

1 Summary and assessment

On acute oral administration, 4-chlorobutanoic acid chloride is harmful (LD_{50} rat oral 1350 and approx. 1510 mg/kg body weight, depending on the source of information) and it is toxic upon inhalation (LC_{50} rat, 4 hours, between 650 and 870 mg/m³). In mice, exposure to 4-chlorobutanoic acid chloride vapours causes sensory irritation of the upper respiratory tract with biphasic impairment of respiratory rate. The concentration which decreases the respiratory rate by 50% (RD_{50}) has been determined as 360 mg/m³ and 260 mg/m³ for short exposure (3 to 10 minutes) and longer exposure (23 to 30 minutes), respectively.

On repeated, 5-time inhalation exposure to 4-chlorobutanoic acid chloride at concentrations ranging from 57.1 to 200.9 mg/m³, considerable loss of weight, impaired breathing and increases in red blood cell counts, haemoglobin concentrations and packed cell volume have been observed to occur in a concentration-dependent manner in rats. A concentration-dependent increase has been seen in the absolute weights of the liver, the kidneys and the spleen. Additionally, the lungs of the male rats of the top concentration group have shown an increase in absolute weight. In a subacute inhalation test lasting 4 weeks, 4-chlorobutanoic acid chloride concentrations of 2, 12 and 60 mg/m³ in rats caused concentration-dependent effects including a retardation in body weight development, impaired breathing, increases in red blood cell counts and packed cell volume, changes in the

absolute and relative weights of some organs (increased absolute and relative lung weights at 60 mg/m³, increased relative kidney weights at 12 mg/m³ and higher, increased absolute and relative weights of the adrenal glands at 60 mg/m³, decreased absolute spleen weights at 60 mg/m³, decreased absolute liver weight at 60 mg/m³ (male rats)) and enlargement of the lungs on exposure to concentrations of 12 and 60 mg/m³. Histopathologically, changes in the mucous membranes of the respiratory tract were seen, with dose-dependent hyperplasia and metaplasia restricted to the more anterior part of the nasal cavity (2 mg/m³) or extending throughout the nasal cavity, the glottis region of the larynx and, focally, the trachea (12 mg/m³) as well as the larger bronchioli (60 mg/m³). At 2 mg/m³, the changes are very slight and can be interpreted as representing a minimum effect (the lowest effective concentration being 2 mg/m³).

The application of the neat substance to the skin and eyes of rabbits produces a very severe corrosive effect. The relevant studies were not conducted according to the present guidelines for testing, but none the less the findings are unequivocal as well as being plausible in the light of the corrosive effects seen with other halogenated acid chlorides.

4-Chlorobutanoic acid chloride shows no mutagenic activity in the Salmonella/microsome test, with or without metabolic activation.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) of the Deutsche Forschungsgemeinschaft will investigate the possibility of establishing a MAK value for the chemical.

2 Name of substance

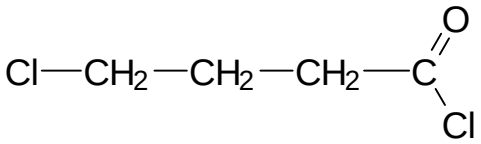
2.1	Usual name	4-Chlorobutanoic acid chloride
2.2	IUPAC name	4-Chlorobutanoic acid chloride
2.3	CAS No.	4635-59-0
2.4	EINECS No.	225-059-1

3 Synonyms, common and trade names

Butanoyl chloride, 4-chloro- (9CI)
Butyryl chloride, 4-chloro- (7CI, 8CI)
4-Chlorbutanoylchlorid
4-Chlorbuttersäurechlorid
4-Chlorbutyrylchlorid
γ-Chlorobutanoic acid chloride
4-Chlorobutanoyl chloride
ϖ-Chlorobutanoyl chloride
4-Chlorobutyric acid chloride
γ-Chlorobutyroyl chloride
4-Chlorobutyroyl chloride
4-Chlorobutyryl chloride
γ-Chlorobutyryl chloride

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_4H_6Cl_2O$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	141.00	
5.2	Melting point, °C	–49 (solidification point)	(BASF, 1991, 1993)
		–47	(Riedel-de Haën, 1995)
5.3	Boiling point, °C	172–174	(Riedel-de Haën, 1995)
		173–174	(BASF, 1993)
		173.5	(Lide and Frederikse, 1996)
		114–116 (at 140 hPa)	(BASF, 1991)
5.4	Vapour pressure, hPa	4 (at 20 °C)	(BASF, 1991, 1993)
		22 (at 50 °C)	(BASF, 1991)

5.5	Density, g/cm³	1.2581 (at 20 °C) (Lide and Frederikse, 1996) 1.26 (at 20 °C) (BASF, 1991, 1993)
5.6	Solubility in water	Decomposes rapidly by hydrolysis to form 4-chlorobutanoic acid and hydrochloric acid (BASF, 1993) Largely hydrolysed after 5 minutes and completely hydrolysed after 30 minutes (BASF, 1997)
5.7	Solubility in organic solvents	Soluble in diethyl ether (Lide and Frederikse, 1996) Miscible with almost all common aprotic organic solvents (BASF, 1989)
5.8	Solubility in fat	No information available
5.9	pH value	Low (acidic) (BASF, 1993)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 5.78 mg/m³ 1 mg/m³ ≙ 0.17 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Intermediate used in the chemical industry for the manufacture of pharmaceuticals, crop protection agents and pesticides, dyestuff precursors and textile auxiliaries (BASF, 1989).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

Acute Toxicity

In exploratory studies in rats, the acute oral LD_{50} was approx. 1510 mg/kg body weight with an observation period of 2 weeks. Administration was ac-

complished using 0.5- to 16-percent aqueous emulsions with carboxymethylcellulose. The clinical signs of toxicity included lying on the stomach, atonia, spasms and dyspnoea. Post-mortems revealed cardiac dilatation, blue-black eschars on the gastric mucosa and diffuse reddening of the intestinal mucosa (BASF, 1973).

In a further acute toxicity study in rats, the LD_{50} was determined as 1350 mg/kg body weight following oral administration of a 4.3- to 92.8-percent solution of the substance in olive oil and a 14-day observation period (male rats approx. 1500 mg/kg body weight, female rats 1210 mg/kg body weight; 5 male and 5 female rats). The LD_{100} was 2150 mg/kg body weight (death occurring within 1 hour), while the LD_0 was 215 mg/kg body weight. The clinical signs of toxicity observed included staggering, tremors, apathy, dyspnoea, atonia, exsiccosis and paresis. Autopsy revealed atrial dilatation of the heart and congestive hyperaemia, acinar pattern of the liver as well as several instances of haemorrhagic eschar formation on the gastric mucosa and pronounced reddening of the intestinal mucosa. All animals sacrificed at the end of the test were found to have adhesions between the forestomach and the spleen, the liver and the peritoneum (BASF, 1980).

Acute inhalation toxicity was studied in accordance with OECD guideline No. 403. Groups of 5 male and 5 female Wistar rats each (average initial weights 317 g and 197 g, respectively) inhaled 4-chlorobutanoic acid chloride (purity of test substance 99.5%) at concentrations of 510, 650 and 870 mg/m³ in a single exposure lasting 4 hours. The observation period was 14 days. The signs of toxicity included laboured breathing, closed eyes, piloerection, hunched posture and during the observation period a deteriorated general condition, irregular breathing, encrustations around the nares, including wounded noses, and encrustations around the eyes. Of all 10 rats exposed to the highest concentration (870 mg/m³), 8 died or had to be killed in extremis in the course of the observation period. No deaths occurred in the other two concentration groups (650 and 510 mg/m³). Body weight was extremely low in most of the animals which died and was also markedly decreased in the surviving animals up to day 7 of observation, though normal weight was regained by day 14 of the observation period. Post-mortems on the deceased rats revealed considerable abnormalities of the lungs (swellings, atelectasis, irregular surface markings, spongy appearance), and some of the rats which were sacrificed at the end of the observation period were found to have greyish, pale or spotted lungs. In addition,

the gastrointestinal tracts of several of the deceased rats were filled with air. The LC_{50} was in the range between 650 and 870 mg/m³ (TNO, 1992).

In an inhalation hazard test (exposure to an atmosphere which was saturated with volatile components of the product at 20 °C), 5 out of 6 rats died after an 8-hour exposure, 3 out of 6 rats after a 3-hour exposure and 1 out of 12 rats after a 1-hour exposure. A 30-minute exposure was survived by 12 rats. The signs of toxicity seen included severe irritation of the mucous membranes, dyspnoea, viscerocranial oedema, oedemas in the joints as well as corrosions of the cornea. Autopsy revealed acute cardiac dilatation and general congestive hyperaemia (BASF, 1973).

4-Chlorobutanoic acid chloride was investigated with respect to sensory irritation using the Alarie test. Male CD®-1 mice (weighing 24 to 29 g) were subjected in groups of 4 animals to single 30-minute exposures to 4-chlorobutanoic acid chloride vapours at concentrations of 150, 320 and 700 mg/m³ of air. In this study, respiratory rates were recorded by means of body plethysmography, differentiating an early phase (minutes 3 to 10) and a late phase (minutes 23 to 30). Exposure time was extended to 1 hour in the top concentration group in order to allow detection of any potential damage to the lower part of the respiratory system. The RD_{50} (concentration leading to a 50-percent decrease in respiratory rate) served as the relevant criterion. It was calculated as percent reduction of the respiratory rates caused by the various concentrations and was found to be 358.1 mg/m³ and 263.0 mg/m³ for the early and late exposure phases, respectively. Following exposure to the highest concentration, the decrease in respiratory rate did not exhibit reversibility in the 10-minute observation period, while it was found to be largely reversible after exposure to 320 and 150 mg/m³ though the initial value was not reached again. The absolute and relative lung weights in the mice exposed to the high concentration (700 mg/m³) showed no significant difference compared with the controls, the conclusion being that 4-chlorobutanoic acid chloride did not cause irritation of the lung under the given experimental conditions. From the results obtained it was concluded that 4-chlorobutanoic acid chloride is an irritant to the upper respiratory tract and that according to the rating system established by Clarke et al. (Pharmacol. Ther., 5, 149–179, 1979) the substance should be classified as causing “light irritancy” in the vaporous state (HRC, 1992).

In the mouse, the LD_{50} was approx. 176 mg/kg body weight following intraperitoneal administration. Lying on the abdomen, dyspnoea, atonia and spasms were observed. Post-mortem findings included obtuse hepatic edges (no further information; BASF, 1973).

Subacute Toxicity

In a preliminary experiment for a subacute toxicity study, groups of 5 male and 5 female Wistar rats (average initial weights 225 and 199 g, respectively) inhaled 4-chlorobutanoic acid chloride (> 99%) at analytically monitored vapour concentrations of 0, 57.1, 100.9 or 200.9 mg/m³ for 6 hours on 5 consecutive days (head-nose exposure). No deaths occurred, but concentration-dependent clinical signs were seen, such as coldness, weakness and impaired breathing, encrustations of the eyelids and occasionally of the nostrils. With respect to body weight, all groups treated with the test substance exhibited dose-dependent weight loss. All male rats showed concentration-dependent increases in red blood cell counts, haemoglobin concentrations and packed cell volume. In the female rats of the top concentration group the red blood cell counts were increased and the average corpuscular haemoglobin content was decreased. A concentration-dependent increase in liver, kidney and spleen weights was seen in all concentration groups, though statistical significance was not reached in all groups (e. g. in the case of the kidneys of the male rats exposed to the low and mid concentrations, and in the case of the livers and spleens of the females exposed to the low concentration), and the male rats of the top concentration group showed an increase in absolute lung weight. The relative lung weights were increased in all concentration groups and the relative kidney weights were increased in the male rats of the high and mid concentration groups. Decreased relative organ weights were found for the livers of the male rats of the high and mid concentration groups as well as for the spleens of rats of both sexes of the top concentration group. Macroscopically, the rats of the mid and high concentration groups were found to have treatment-related changes in the gastrointestinal tract (dilatation of (parts of) the gastrointestinal tract; stomach, caecum, small intestines and/or colon filled with a yellow liquid), in the lungs (swollen, spotted, spongy-like lungs, rough pleural surface, focal atelectasis), in the liver (small) as well

as on the skin and fur (nasal encrustations, soiled or grey discoloured fur). The no toxic effect level was given as < 57.1 mg/m³ (TNO, 1993).

The subacute inhalation toxicity was studied by subjecting groups of 5 male and 5 female Wistar rats (initial weights 229 and 166 g, respectively) to 4-chlorobutanoic acid chloride (> 99%) at concentrations of nominally 0 mg/m³ (controls), 2, 12 and 60 mg/m³ (head-nose exposure). The analytically determined actual concentrations were 2.1, 11.8 and 59.1 mg/m³. The investigations were carried out according to OECD guideline No. 412, with exposure times of 6 hours a day, 5 times per week for a period of 4 weeks. No deaths occurred. The clinical signs seen in all animals of the high concentration group included irregular breathing and, in the further course of the study, sniffing and sneezing noises, which were also observed in some of the rats of the mid concentration group. Body weight gain was retarded in the male rats of the high and mid concentration groups and in the female rats which were exposed to the top concentration. Food intake by the male rats of the high concentration group was reduced throughout the entire period of exposure, the female rats in this group showing reduced intakes during the first three weeks of the study. Haematology results showed increases in the numbers of red blood cells and packed cell volume in rats of both sexes of the top concentration group, with the male rats of this group additionally exhibiting an increase in haemoglobin content. Furthermore, decreased numbers of lymphocytes were seen, whilst the numbers of neutrophils were increased. The clinical chemistry results showed a concentration-dependent increase in aspartate aminotransferase activity in the male rats of the top and mid concentration groups. Further clinical-chemical findings included increased total protein content in the male rats of the top concentration group, a decreased albumin-globulin ratio in the male rats of the top concentration group and the females of the mid and top concentration groups as well as elevated sodium levels in the male rats of the top concentration group. The absolute and relative lung weights and the relative kidney weights were increased in the rats of the top concentration group. In the male rats of the mid concentration group the relative kidney weights were also higher than in the controls. The female rats of the high concentration group had increased absolute and relative adrenal weights, whilst the male rats showed increased relative adrenal weights. Both sexes were found to have decreased absolute spleen weights at the high concentration. In addition, the male rats of the high concentration group exhibited

a decrease in absolute liver weight. Autopsy revealed enlargement of the lungs in the rats of the high and mid concentration groups. Histopathological examination disclosed primarily treatment-related changes in the respiratory tract. They consisted in epithelial hyperplasia and metaplasia in all concentration groups, with rats of both sexes of the mid and high concentration groups and the male rats of the lowest concentration group also showing inflammatory changes. The severity of the changes increased with the concentration of the test compound. In the rats of the lowest concentration group they were limited to the anterior part of the nasal cavity (transitional and ciliated respiratory epithelium; severity: very slight to slight). In the mid concentration group the entire nasal cavity was affected, as were the glottis region of the larynx and, focally, the trachea (severity: very slight to moderate). In the top concentration group, larger bronchioli were also affected (severity: very slight to severe). A no effect level was not reached in this study. A concentration of 2.1 mg/m³ was given as the minimum effect level for 4-chlorobutanoic acid chloride (TNO, 1996).

7.3 Skin and mucous membrane effects

In less recent exploratory studies, 4-chlorobutanoic acid chloride produced slight reddening when applied to the dorsal skin of rabbits for one minute. Subsequent to exposure for 5 minutes, severe necrosis was observed and 15-minute and 20-hour exposures caused deep necrosis down to the muscle. Application to the rabbit ear followed by a 20-hour exposure led to loss of the ear after 8 days (BASF, 1973). The substance hence proved severely corrosive to the skin.

Instillation of 50 mg 4-chlorobutanoic acid chloride into the conjunctival sac of the rabbit eye led to severe oedema and corneal clouding as well as burns of the nictitating and mucous membranes. After 24 hours the effects were more severe. In addition, eyelid necrosis with suppurating secondary infections developed after 8 days (BASF, 1973). The substance thus exhibited severe corrosive effects on the eye.

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

4-Chlorobutanoic acid chloride (purity of the test substance approx. 99 %) was tested in the Salmonella/microsome test (standard-plate incorporation test) using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, with and without metabolic activation (S9-mix from Aroclor 1254-induced rat liver) in the concentration range from 20 to 5,000 µg/plate. No increase in the revertant counts was observed with or without metabolic activation. Concentrations of ≥ 750 µg/plate proved toxic to bacteria (BASF, 1981).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

No information available.

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

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) of the Deutsche Forschungsgemeinschaft will investigate the possibility of establishing a MAK value for the chemical (DFG, 2000).

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