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BG RCI
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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Chloroformic acid propyl ester

No. 159

CAS No. 109-61-5

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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Chloroformic acid propyl ester

Apart from the evaluation of chloroformic acid propyl ester (No. 159), there are also TOXICOLOGICAL EVALUATIONS of chloroformic acid methyl ester (No. 36), chloroformic acid ethyl ester (No. 77) and chloroformic acid butyl ester (No. 160), which may be consulted for comparison.

1 Summary and assessment

Chloroformic acid propyl ester is harmful upon acute oral administration (LD_{50} rat oral for a solution of the chemical in oil: 1212.4 mg/kg body weight). An LD_{50} determination using an aqueous formulation of the chemical, for which the possibility of hydrolysis can not be precluded, gave a lower oral LD_{50} value of approx. 872 mg/kg body weight for the rat. Upon inhalation, chloroformic acid propyl ester is clearly toxic. A 1-hour exposure to 200 ppm (approx. 1000 mg/m³) was lethal to 3 out of 10 rats while in an inhalation hazard test all rats died following a 3-minute exposure to atmosphere which was enriched or saturated with vapour at 20 °C. In the absence of further details, it has been reported that the LC_{50} for 1-hour exposure is 1600 mg/m³. It has also been reported, again without providing further details, that the LD_{50} for dermal application is > 10200 mg/kg body weight. However, dermal application results in severe irritation and corrosion of the skin (see below). The signs of toxicity observed after acute oral administration include dyspnoea, apathy, abnormal position, reeling, tremor, rough coat, cyanosis and poor general condition. Upon inhalation exposure, the signs of toxicity, consisting in extremely severe mucous membrane irritation, gasping and dyspnoea, are determined by the agent's corrosive effects. As regards the necropsy findings, it is again the corrosive effects of chloroformic acid propyl ester that are predominant. Oral administration of lethal doses to rats results in necrotic white gastrointestinal mucosa, and acute intoxication by inhalation leads to congestion and oedema of the lungs and acute pulmonary emphysema. In addition, findings following oral administration of lethal doses also include acute dilation and congestive hyperaemia of the heart. Following oral administration of sublethal doses > 147 mg/kg body weight, the occurrence has been reported of adhesions between the forestomach and the spleen, liver and peritoneum and diverticularisation of the forestomach with scabs or crusts.

Chloroformic acid propyl ester has a severely irritating and corrosive effect on the skin and eyes of rabbits. Even a 1-minute skin exposure causes slight necrosis.

Conducted as a preincubation test, the Salmonella/microsome test on *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 revealed no mutagenic potential for chloroformic acid propyl ester either in the absence or presence of metabolic activation.

2 Name of substance

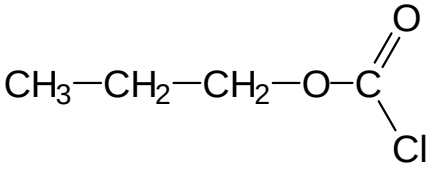
2.1	Usual name	Chloroformic acid propyl ester
2.2	IUPAC name	Chloroformic acid n-propyl ester
2.3	CAS No.	109-61-5
2.4	EINECS No.	203-687-7

3 Synonyms, common and trade names

Carbonochloridic acid, propyl ester
Chlorameisensäurepropylester
Chlorameisensäure-n-propylester
Formic acid, chloro-, propyl ester
n-Propylchlorformiat
n-Propylchlorkohlensäureester
Propyl chlorocarbonate
Propyl chloroformate
n-Propyl chloroformate

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_4H_7O_2Cl$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	122.55	
5.2	Melting point, °C	< –70	(BASF, 1998)
5.3	Boiling point, °C	57.5 (at 133 hPa) 25.3 (at 267 hPa) 112.4 (at 1013 hPa) 115 (at 1013 hPa) 114–115 (1023 hPa) 115.2	(Damle, 1992) (Böhm, 2001) (Sax, 1995) (Lide and Frederikse, 1996)
5.4	Vapour pressure, hPa	26 (at 20 °C)	(BASF, 1998)
5.5	Density, g/cm³	1.090 (at 20 °C) 1.0901 (at 20 °C) 1.091 (at 20 °C) 1.09202 (at 20 °C)	(Sax, 1995) (Lide and Frederikse, 1996) (Damle, 1992) (Böhm, 2001)
5.6	Solubility in water	Insoluble, decomposition by hydrolysis	(Damle, 1992; Sax, 1995)
5.7	Solubility in organic solvents	Miscible with ethanol, ether and benzene	(Lide and Frederikse, 1996; Sax, 1995)
5.8	Solubility in fat	No information available	
5.9	pH value	No information available	
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 5 mg/m³ 1 mg/m³ ≙ 0.2 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

Versatile intermediate used in the chemical industry, particularly in the manufacture of pesticides and pharmaceuticals (BASF, 1988 a, 1991; Damle, 1992).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

The acute toxicity data for chloroformic acid propyl ester following oral, inhalation, dermal and intraperitoneal administration are summarised in Table 1.

Beginning of Table 1

Table 1. Acute toxicity studies of chloroformic acid propyl ester						
Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	observation period	Reference
Rat, Sprague-Dawley, male, female	oral	1212.4, administered as 2–63.2% solutions in olive oil	n. d.	LD_{50}; dyspnoea, apathy, abnormal position, reeling, tremor, rough coat, cyanosis, poor general condition and, occasionally, rattling respiration, aggressive behaviour, exsiccosis, salivation and gasping; necropsy findings in animals that died intercurrently at dose levels of 681 mg/kg body weight and above: acute right heart dilation and acute congestive hyperaemia of the heart, necrotic white mucosa of the stomach (necrotic corrosive gastritis) and intestine; terminal necropsy: dose levels ≤ 147 mg/kg body weight were without findings; findings at higher dose levels included diverticularisation of the forestomach and partly scabs or crusts and also partly adhesions between the forestomach and the spleen, liver and peritoneum	14 days	BASF, 1980
Rat	oral	ca. 872 (800 mm³), administered as a 0.1–20% aqueous tragacanth gum emulsion	n. d.	LD_{50}; dyspnoea, reeling, lying on the abdomen, apathy; necropsy findings: adhesive-inflammatory processes in the stomach wall	14 days	BASF, 1970
n. d.	oral	650	n. d.	LD_{50}	n. d.	Damle, 1992
n. d.	inhalation	1600 (320 ppm), one hour	n. d.	LC_{50}	n. d.	Damle, 1992
Rat	inhalation	atmosphere enriched or saturated with vapour at 20 °C	n. d.	mortality: 12/12; vigorous escape behaviour, extremely severe mucous membrane irritation, gasping; necropsy findings: congestion and oedema of the lungs	n. d.	BASF, 1970
Rat	inhalation	ca. 1000 (200 ppm), one hour	n. d.	mortality: 3/10; restlessness, mucous membrane irritation,	n. d.	BASF, 1970

Table 1. Acute toxicity studies of chloroformic acid propyl ester						
Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	observation period	Reference
				dyspnoea; necropsy findings: acute emphysema of the lungs		
n. d.	dermal	> 10200	n. d.	LD_{50}	n. d.	Damle, 1992
Mouse	intraperitoneal	ca. 16 (15 mm³), administered as a 0.1–20% aqueous tragacanth gum emulsion	n. d.	LD_{50}; dyspnoea, reeling, tremor, lying on the abdomen, apathy; necropsy findings: adhesions in the abdominal cavity	14 days	BASF, 1970

[1] where specified
n. d. no data

End of Table 1

When administered orally to rats, chloroformic propyl ester formulated in olive oil was found to have an LD_{50} value of 1212 mg/kg body weight, and thus proved to be harmful (BASF, 1980). Upon inhalation, chloroformic acid propyl ester was clearly toxic. A 1-hour exposure to 200 ppm (approx. 1000 mg/m³) was lethal to 3 out of 10 rats while in an inhalation hazard test all rats died following a 3-minute exposure to atmosphere which was enriched or saturated with vapour at 20 °C (BASF, 1970). Dyspnoea, apathy, abnormal position, reeling, tremor, rough coat, cyanosis and poor general condition were described as signs of toxicity noted in a large number of animals following oral administration (BASF, 1970, 1980). Upon inhalation exposure, the signs of toxicity, which consisted in extremely severe mucous membrane irritation, gasping and dyspnoea, were determined by the agent's corrosive effects (BASF, 1970). Necropsy findings also, in particular, included changes that were attributable to the chemical's corrosive properties, with inhalation exposure being associated with considerable congestion and oedema of the lungs or pulmonary emphysema and oral administration of lethal doses resulting in necrotic corrosive gastritis. In addition, findings following oral administration of lethal doses also included acute atrial dilatation and acute congestive hyperaemia of the heart. Upon oral administration of sublethal doses > 147 mg/kg body weight, the rats' forestomachs exhibited diverticularisation and scabs or crusts, and partly there were adhesions between the forestomach and the spleen, liver and peritoneum (BASF, 1970, 1980).

Chloroformic acid propyl ester undergoes hydrolysis in aqueous solution (see also Section 5.6). Therefore, the oral LD_{50} values determined for

aqueous tragacanth gum emulsions of chloroformic acid propyl ester (rat oral approx. 872 mg/kg body weight and mouse intraperitoneal approx. 16 mg/kg body weight; BASF, 1970) are suitable only to a limited extent for the assessment of the chemical's acute toxicity, as the possibility can not be precluded that the test substance contained in those formulations was partially hydrolysed. The LD_{50} and LC_{50} values reported in a review article as secondary data (oral 650 mg/kg body weight, dermal > 10200 mg/kg body weight, and 1600 mg/m³ for 1-hour inhalation exposure; Damle, 1992) are unsuitable for the assessment of the acute toxicity of chloroformic acid propyl ester, as no details are given regarding either the species investigated or the experimental conditions.

7.3 Skin and mucous membrane effects

The acute skin irritancy of undiluted chloroformic acid propyl ester (purity not specified) was tested in rabbits. The chemical was applied to the dorsal skin for 1, 5 or 15 minutes or 20 hours, or to the skin of the ear for 20 hours. The observation period was 8 days. As shown in Table 2 below, the treated skin exhibited severe irritation and corrosion which was dependent upon the duration of exposure to chloroformic acid propyl ester. Necrosis occurred even when the duration of exposure was only 1 minute (BASF, 1970).

Table 2. Irritant effects of chloroformic acid propyl ester on the rabbit skin and their dependence on the duration of exposure (based on BASF, 1970)

Application site	Duration of exposure	Findings after 24 hours	Findings after 8 days
Back	1 minute	severe reddening, mild oedema, degeneration in some cases	slight necrosis, severe oedema
Back	5 minutes	very severe reddening, severe oedema, haemorrhages, brown degeneration	slight necrosis, severe oedema, severe reddening
Back	15 minutes	very severe reddening, severe oedema, haemorrhages, brown degeneration	severe necrosis, severe oedema, very severe reddening
Back	20 hours	slight necrosis, severe oedema, severe reddening	sever necrosis, severe oedema, slight reddening
Ear	20 hours	slight reddening, severe oedema, bluish discoloration	severe necrosis, severe oedema

Chloroformic acid propyl ester exhibited corrosive effects to the eye in a rabbit study. At one hour and at 24 hours following instillation of 50 µl chloroformic acid butyl ester (purity not specified) into the rabbit eye, severe

reddening, very severe oedema and severe clouding of the eye were observed. At 8 days, corrosive effects were even more manifest, with severe oedema, severe clouding and haemorrhages being observed. Negative controls treated with sodium chloride were without abnormal findings at all scheduled examinations (BASF, 1970).

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

In the Salmonella/microsome test carried out in accordance with OECD guideline No. 471, chloroformic acid propyl ester (purity > 99%) was devoid of mutagenicity both in the absence and presence of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver). The study was conducted as a preincubation test in which *Salmonella typhimurium* strains TA 98, TA 100 and TA 1537 were incubated with chloroformic acid propyl ester at concentrations from 0.0005 to 0.5 µl/plate, *Salmonella typhimurium* strain TA 1535 being exposed to chloroformic acid propyl ester levels ranging from 0.0005 to 5.0 µl/plate. Ethanol served as the solvent. In the presence of S-9 mix concentration levels ≥ 0.3 µl/plate exhibited bacteriotoxicity while in the absence of metabolic activation even lower concentrations ≥ 0.002 µl/plate were toxic. Incubation of *Salmonella typhimurium* strains with chloroformic acid propyl ester did not result in any significant increase in revertant counts. Tests with the positive controls 2-aminoanthracene, N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylenediamine, 9-aminoacridine chloride monohydrate and dimethylcarbamyl chloride gave the expected results (BASF, 1988 b).

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

No information available.

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