The BG RCI is the legal successor of BG Chemie since 2010

BG RCI
Berufsgenossenschaft
Rohstoffe und chemische Industrie

TOXICOLOGICAL EVALUATIONS

BG RCI

Kurfürsten-Anlage 62 · D-69115 Heidelberg, Germany
Telefon: +49 6221 5108-28451
E-Mail: toxikologischebewertungen@bgrci.de
Internet: www.bgrci.de/toxicologicalevaluations

TOXICOLOGICAL EVALUATION

last updated: 02/2005

Dichloro-acetyl chloride

No. 188 a

CAS No. 79-36-7

BG Chemie
Berufsgenossenschaft der chemischen Industrie

BG Chemie
P.O.B. 10 14 80, 69004 Heidelberg, Germany
Telephone: +49 (0) 6221 523 400
E-Mail: ToxikologischeBewertungen@bgchemie.de
Internet: www.bgchemie.de/toxicologicalevaluations

Dichloroacetyl chloride

Dichloroacetyl chloride is hydrolysed to dichloroacetic acid and hydrochloric acid in the presence of water. Therefore, at least part of the toxicological effect of dichloroacetyl chloride is likely to be attributable to the products of hydrolysis. A Toxicological Evaluation on dichloroacetic acid and sodium dichloroacetate (No. 188 b) has also been published.

1 Summary and assessment

Dichloroacetyl chloride is of low oral toxicity but harmful following dermal exposure in the available animal acute toxicity studies (LD_{50} rat oral between 2450 and 4450 mg/kg body weight; LD_{50} rabbit dermal 650 mg/kg body weight). In older studies, 2 out of 6 rats died after single 4-hour exposure to a nominal concentration of 2000 ppm dichloroacetyl chloride (equivalent to 12 mg/l). Four-week oral administration of 222.5 mg/kg body weight/day to male rats or 127 mg/kg body weight/day to female rats did not result in substance-related changes in the liver or kidney.

In the rabbit, dichloroacetyl chloride leads to full-thickness destruction of the skin after 3 minutes' exposure and must therefore be considered to be severely corrosive.

Dichloroacetyl chloride was not mutagenic in the absence or presence of metabolic activation when tested in the Salmonella/microsome assay using *Salmonella typhimurium* and *Escherichia coli* WP2uvrA in a standard plate incorporation assay. However, the chemical caused a marked increase in revertant counts in a Salmonella/microsome preincubation assay using strain TA 100 in the absence of metabolic activation.

The available literature data from carcinogenicity studies of dichloroacetyl chloride following dermal, subcutaneous or inhalation exposure do not comply with current requirements. However, in view of the findings, it cannot be excluded that the chemical has a carcinogenic potential.

In humans, dichloroacetyl chloride air levels of approx. 10 ppm cause respiratory tract irritation.

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 listed dichloroacetyl chloride in the "Yellow Pages" (Substances being Examined for the Establishment of MAK Values and BAT Values") of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie is order that the carcinogenic effect be examined.

2 Name of substance

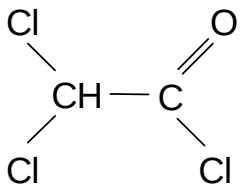
2.1	Usual name	Dichloroacetyl chloride
2.2	IUPAC name	Dichloroacetyl chloride
2.3	CAS No.	79-36-7
2.4	EINECS No.	201-199-9

3 Synonyms, common and trade names

Dichloracetylchlorid
α,α-Dichloracetylchlorid
2,2-Dichloracetylchlorid
Dichloressigsäurechlorid
Dichlorethanoylchlorid
2,2-Dichlorethansäurechlorid
Dichloroacetic acid chloride
2,2-Dichloroethanoic acid chloride

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula C_2HCl_3O

5 Physical and chemical properties

5.1	Molecular mass, g/mol	147.39
5.2	Melting point, °C	No information available
5.3	Boiling point, °C	106–108 (Hoechst, 1990) 107 (at 1013 hPa) (Koenig et al., 1986) 108 (Lide and Frederikse, 1996)
5.4	Vapour pressure, hPa	30.6 (at 20 °C) (Koenig et al., 1986; Hoechst, 1990)
5.5	Density, g/cm³	1.531 (at 20 °C) (Hoechst, 1990) 1.5315 (at 16 °C) (Koenig et al., 1986; Lide and Frederikse, 1996)
5.6	Solubility in water	Hydrolysis (Windholz et al., 1983; Lide and Frederikse, 1996)
5.7	Solubility in organic solvents	Miscible with diethyl ether, decomposes in ethanol (Windholz et al., 1983; Lide and Frederikse, 1996)
5.8	Solubility in fat	No information available
5.9	pH value	–
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 6.02 mg/m³ 1 mg/m³ ≙ 0.17 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Industrial intermediate in the manufacture of dichloroacetic acid, dichloroacetic anhydride and dichloroacetic acid esters; used in the manufacture of pharmaceuticals and crop protection agents (Koenig et al., 1986).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

The oral LD_{50} of dichloroacetyl chloride determined in male Wistar rats (weighing 90 to 120 g) after a 14-day observation period was 2460 (1830 to 3230) mg/kg body weight (no further details; Smyth et al., 1951).

Groups of 10 female SPF-Wistar rats (mean initial weight 109 g) received a single dose of dichloroacetyl chloride as a 10-percent solution in sesame oil at levels from 500 to 2000 mg/kg body weight by oral gavage. The observation period was 2 days. Doses of 500 and 800 mg/kg body weight were survived by all rats, whereas 3 out of 10 and 10 out of 10 died after 1250 and 2000 mg/kg body weight, respectively (no clinical signs reported). Necropsy of the deceased animals revealed severe corrosion of the gastrointestinal tract with sites of perforation (Hoechst, 1967 a).

One publication reported oral LD_{50} values of 4450 and 2540 mg/kg body weight for male and female rats, respectively (English abstract; Rosca et al., 1982).

In rabbits, occlusive dermal application resulted in an LD_{50} of 650 (530 to 810) mg/kg body weight after a 14-day observation period (no further details; Smyth et al., 1951).

Dichloroacetyl chloride was tested in rats in the inhalation hazard test with a 14-day observation period. A single 8-minute inhalation exposure to the fraction that was volatile at room temperature was survived by all 6 rats. A single 4-hour exposure to a nominal concentration of 2000 ppm dichloroacetyl chloride (equivalent to 12040 mg/m³) was fatal to 2 out of 6 rats within an observation period of 14 days (no further details; Smyth et al., 1951).

Groups of 3 male and 3 female albino mice in a 28-litre glass bell jar were given a single exposure to dichloroacetyl chloride vapour for a maximum of one hour. A volume of 1, 0.5 or 0.1 ml of the chemical was evaporated in the bell jar. Vapour concentrations were not determined analytically. Mice exposed to the highest concentration showed rubbing of the eyes and eyelid closure after only one minute. They died after 3 to 15 minutes, exhibiting gasping respiration and convulsions. Necropsy revealed congestion of the lungs. The intermediate concentration caused the same clinical signs, and 3 out of 6 animals died after 8 to 15 minutes, exhibiting gasping respiration

and convulsions. Necropsy again revealed congestion of the lungs. The behaviour of the 3 surviving mice was normal during the 7-day observation period. At the low concentration, the animals showed severe excitation and rubbing of the eyes after approx. 2 minutes. Exposure was terminated after one hour. The 6 mice exhibited normal behaviour during the 7-day observation period (Hoechst, 1967 b).

Dichloroacetyl chloride was administered orally as an oily solution to groups of 5 male Wistar rats at 44.5 or 222.5 mg/kg body weight/day and groups of 5 females at 25.4 or 127 mg/kg body weight/day (equivalent to 1/100 and 1/20 of the oral LD_{50}) over a period of 28 days. Five males and 5 females served as controls. Neither the kidneys nor the liver showed any substance-related histopathological changes (no further details; Rosca et al., 1982; Szövérfi et al., 1983).

7.3 Skin and mucous membrane effects

The skin irritancy of dichloroacetyl chloride (97% pure) was tested in 2 New Zealand albino rabbits (weighing 2.2 and 2.8 kg) in accordance with OECD guideline for testing No. 404. The animals had a single 0.5 ml dose of the undiluted product applied to the mechanically depilated skin of the dorsal trunk. Exposure lasted 4 hours in one animal and 3 minutes in the other. Complete destruction of the treated skin resulted in both cases. Based on these findings, dichloroacetyl chloride was evaluated as severely corrosive (Hoechst, 1988 a).

Application of as little as 10 mg dichloroacetyl chloride to the clipped abdominal skin of rabbits produced moderate irritation after 24 hours' exposure (no further details; Smyth et al., 1951).

Instillation of 50 µg dichloroacetyl chloride into the conjunctival sac of the rabbit caused very severe eye irritation (no further details; Smyth et al., 1951).

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

Dichloroacetyl chloride (approx. 97% pure) was tested for mutagenic activity in the Salmonella/microsome assay (standard plate incorporation assay) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and *Escherichia coli* WP2uvrA in the absence and presence of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver). Concentration levels of 4, 20, 100, 500, 2500 and 10000 µg/plate (dissolved in DMSO) were tested in two independent trials with 3 plates/concentration. Concentrations of and above 500 µg/plate were toxic to the bacteria. Dichloroacetyl chloride produced no increase in revertant counts in the presence or absence of metabolic activation and therefore proved not to be mutagenic (Hoechst, 1988 b).

Dichloroacetyl chloride (97% pure) was further tested for its mutagenic activity in the Salmonella/microsome assay with preincubation using *Salmonella typhimurium* strains TA 98 and TA 100 in the absence and presence of metabolic activation (S-9 mix from Aroclor 1254-induced rat or hamster liver). The test concentrations were in the range from 3 to 6666 µg/plate. Strain TA 98 showed no increase in revertant count up to the highest concentration in the presence or absence of metabolic activation, whereas strain TA 100 showed a concentration-dependent increase in revertant counts which exceeded that of the positive controls (sodium azide) from 1000 µg/plate in the absence of metabolic activation. The highest concentration was toxic to the bacteria (Zeiger et al., 1992).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

Female mice (ICR-Ha Swiss) aged 6 to 8 weeks had 0.1 ml acetone containing dichloroacetyl chloride (> 99% pure) applied to the shaved dorsal

skin (area of application not reported) three times per week over periods varying from 82 to 94 weeks. Positive controls received dimethylcarbamyl chloride. The exposure regimen is shown in Table 1.

Table 1. Dermal carcinogenicity study of dichloroacetyl chloride in the mouse

Dosage	Number of animals	Duration of test (days)	Median survival time (days)
Control groups			
Dimethylcarbamyl chloride			
2.0 mg/animal/administration	50	615	475
Acetone			
0.1 ml/animal/administration	30	575	> 575
0.1 ml/animal/administration	30	610	> 610
0.1 ml/animal/administration	50	665	515
Dichloroacetyl chloride			
0.25 mg/animal/administration	30	576	> 576
1.5 mg/animal/administration	30	660	485
3.0 mg/animal/administration	50	660	520

The high dose level corresponded to the maximum tolerated dose which produced little or no irritation of the skin at the site of administration (no further details), no clinical signs and no effects on body weight gain in a 6- to 8-week preliminary study in groups of 5 animals/dose level. For further confirmation of the doses selected, sections were taken from the area of administration and the liver and examined histopathologically for each dose group. The animals in the main study were shaved at the beginning of the study and then as needed. They were examined daily for tumours and weighed at 30- to 60-day intervals. Tissues from all animals that died intercurrently or were sacrificed at study termination underwent histopathological examination, including the lung, liver, kidney, spleen, colon, urinary bladder, area of administration and any other tissues or organs that appeared clinically abnormal. The median survival times are shown in Table 1. The solvent controls and the treated groups exhibited no tumours in the area of administration or any other tissue or organ that was examined. No body weight data or clinical signs were reported for the animals in the main study (Van Duuren et al., 1983, 1987).

The same investigators also treated 6- to 8-week-old female ICR/Ha Swiss mice (30 or 50 animals/group) once weekly with dichloroacetyl chloride (> 99% pure), dissolved in tricaprylin or trioctanoin, at dose levels of 0.05 or 2.0 mg/animal/administration by subcutaneous injection into the left flank

(0.05 ml injection volume). The administration period was 80 to 94 weeks. Positive controls were injected with dimethylcarbamyl chloride. The high dose level corresponded to the maximum tolerated dose which produced little or no irritation of the skin at the site of administration (no further details), no clinical signs and no effects on body weight gain in a 6- to 8-week preliminary study in groups of 5 animals/dose level. For further confirmation of the doses selected, sections were taken from the area of administration and the liver and examined histopathologically for each dose group. The animals in the main study were examined daily for tumours and weighed at 30- to 60-day intervals. Tissues from all animals that died intercurrently or were sacrificed at study termination underwent histopathological examination, including the lung, liver, kidney, spleen, colon, urinary bladder, area of administration and any other tissues or organs that appeared clinically abnormal. Median survival time, administration period and number and type of tumour at the site of administration are presented in Table 2.

Table 2. Median survival time, administration period and incidence of local tumours following chronic subcutaneous injection of dichloroacetyl chloride in mice

Dosage	No. of animals	Median survival time/test duration (days)	Number of animals with tumours at the site of administration	Type of tumour at the site of administration
Control groups				
0.43 mg/animal/administration dimethylcarbamyl chloride	30	> 585/585	9	3 sarcomas 6 haemangiomas
4.3 mg/animal/administration dimethylcarbamyl chloride	30	405/585	22	19 sarcomas 2 squamous carcinomas 1 papilloma
4.3 mg/animal/administration dimethylcarbamyl chloride	50	305/365	42	37 sarcomas 3 squamous carcinomas 1 papilloma
0.05 ml/animal/administration tricaprylin	30	> 524/561	0	–
0.05 ml/animal/administration trioctanoin	30	> 595/595	0	–
0.05 ml/animal/administration trioctanoin	50	> 525/560	0	–
0.05 ml/animal/administration trioctanoin	50	490/660	2	2 haemangiomas
Dichloroacetyl chloride				
2.0 mg/animal/administration in trioctanoin	50	510/660	4*	1 sarcoma 1 squamous carcinoma 1 papilloma 1 haemangioma
0.05 mg/animal/administration in tricaprylin	30	> 560/560	1	1 fibrosarcoma
* Significantly different from the controls				

At a dose of 0.05 mg/animal 1 out of 30 mice developed a fibrosarcoma at the site of administration (0 out of 130 controls) and at a dose of 2.0 mg/animal 1 out of 50 mice developed a sarcoma and 1 out of 50 a squamous carcinoma (0 out of 30 controls). The incidences of all other tumours were within the range of the control group (no further details). Body weight gains and the animals' behaviour were not reported. The investigators considered the observed increase in the incidence of tumours at the site of administration to be indicative of the chemical's possible tumorigenic potential (Van Duuren et al., 1983, 1987).

In addition, dichloroacetyl chloride was investigated for its carcinogenic activity in an inhalation study in 9- to 10-week-old male Sprague-Dawley rats (body weight 325 ± 16.8 g) together with four other alkylating agents (β-propiolactone, methyl methanesulphonate, ethyl chloroformate and propylene oxide). The study was conducted because earlier rat inhalation studies (6 hours/day, 5 days/week) of water-reactive compounds (bis(chloromethyl) ether, epichlorohydrin and dimethylcarbamyl chloride) had found increases in nasal tumours, with the carcinogenic potency of the agents being inversely proportional to their chemical reactivity. Hydrolysis rate served as the measure of chemical reactivity. Animals underwent whole-body exposure for 6 hours/day on 5 days/week in dynamic exposure chambers (1.0 or 1.3 m^3) a total of 30 times. The concentrations tested were inversely proportional to the rates of hydrolysis of the compounds. Chamber concentrations were analysed by IR spectroscopy at half-hour intervals. All animals were observed daily and weighed monthly until their spontaneous death. Several rats had to be sacrificed in moribund condition. All animals were necropsied. The nasal passages were then flushed with formalin and the entire head and other organs fixed in the same fixative. Subsequently, the head was decalcified and stepwise cross-sections were taken in the dorsoventral plane of the anterior portion of the skull. Additionally, light microscopy studies were performed on the larynx, trachea, each lobe of the lung, liver, kidneys, testes and any other organs exhibiting gross pathology. Table 3 summarises the tumorous and non-tumorous lesions of the nose and the numbers of tumours in other organs found for dichloroacetyl chloride, the agent with the highest hydrolysis rate ($T_{½}$ = 0.004 minutes, determined at –20 °C), in comparison with the data for β-propiolactone (5 and 10 ppm), which has an intermediate hydrolysis rate ($T_{½}$ = 60 minutes), and methyl methanesulphonate, which is hydrolysed at

a relatively low rate ($T_{½}$ = 580 minutes). Tables 4 and 5, respectively, list by type of tumour the malignant and benign tumours diagnosed in organs other than the nose. The alkylating agents primarily induced lesions in the upper respiratory tract, particularly in the anterior portion of the nose at the nasomaxillary turbinates, the lateral nasal walls, the nasal septum and the olfactory epithelium in the dorsal meatus. The lesions (necrosis, ulceration and acute inflammation) were more pronounced in the respiratory epithelium than in the squamous or olfactory epithelium. Some animals developed squamous metaplasia and dysplastic lesions, leading to tumorigenesis. High incidences of nasal tumours occurred among rats from the 5 and 10 ppm β-propiolactone groups and rats from the 50 ppm methyl methanesulphonate group. In contrast, the group exposed to the highest dichloroacetyl chloride level (2 ppm) had only a low incidence of nasal tumours. Approximately 20% of rats exposed to low concentration levels of dichloroacetyl chloride (0.5 or 1.0 ppm) developed squamous metaplasia in the nose, but no benign or malignant tumours. None of the alkylating agents induced tumours in the larynx or trachea. The mucosa with the olfactory epithelium in the ethmoidal regions of the posterior nasal cavity also developed rhinitis but no tumours. The lungs of old rats were noticed to contain bronchiectasis and acute pneumonic lesions, and nearly all animals that died had severe rhinitis with seropurulent exudate. Dichloroacetyl chloride, which hydrolyses very rapidly, induced nasal tumours only at a very low incidence. In the investigators' interpretation, this reflected that it was unlikely that sufficient amounts of unchanged dichloroacetyl chloride would survive transit across the aqueous media in the nasal mucosa to target DNA. Electrophilic compounds with very rapid hydrolysis rates would, therefore, be less carcinogenically potent than originally expected because of competing reactions with these compounds by water and nucleophiles other than DNA (Sellakumar et al., 1987). Even without statistical analysis it is evident from the tabular listings (Tables 4 and 5) of malignant and benign tumours noted in organs other than the nose that dichloroacetyl chloride and the two alkylating agents tested in parallel, β-propiolactone and methyl methanesulphonate, did not induce tumours in those organs at a rate higher than that seen in the concurrent air controls. The neoplasms observed in the treatment groups largely corresponded in location and tumour type to the spontaneous tumours diagnosed among the concurrent control group. The absence of neoplasms among the non-nasal tumours in the group exposed to 10 ppm β-propiolactone is attributable to the consid-

erably shorter survival time of those rats (median survival time 362 days) as compared with survivals of the air control and the other exposed groups, which had median life spans between 495 and 652 days. The alkylating agents tested thus acted as local carcinogens in rats in the inhalation studies discussed. As also discussed by the investigators, dichloroacetyl chloride proved to be the least potent carcinogen under the experimental conditions used.

Dichloroacetyl chloride (> 99% pure) was also tested in an initiation/promotion carcinogenicity study in which phorbol myristate acetate (PMA) was used as a promoter in 6- to 8-week-old female ICR/Ha Swiss mice. Fifty animals each had a single dose of 0.1 ml acetone containing 3 mg dichloroacetyl chloride as the initiator applied to the shaved dorsal skin. After a treatment-free period of 2 weeks, 0.1 ml of the promoter phorbol myristate acetate in acetone was applied thrice weekly over a period of 640 days to the skin, which was shaved as needed. Serving as controls, 2 groups comprising 50 and 30 animals were treated in the same manner with 0.1 ml acetone containing 0.0025 or 0.005 mg phorbol myristate acetate, respectively. Positive controls (50 animals) received dimethylcarbamyl chloride. Histopathology was performed on tissues from all animals that died intercurrently or were sacrificed at study termination, including the lung, liver, kidney, spleen, colon, urinary bladder, area of administration and any other tissues or organs that appeared abnormal. The data on median survival time, tumour incidence and type of tumour at the site of administration are summarised in Table 6.

Table 6. Initiation/promotion study of dichloroacetyl chloride in mice

Dose*	No. of animals	Median survival time/test duration (days)	Number of animals with tumours at the site of administration	Appearance of first tumour (study day)
Control groups				
Phorbol myristate acetate				
0.0025 mg/animal	50	455/635	0	–
0.005 mg/animal	30	> 490/490	3**	420
Dichloroacetyl chloride*				
3.0 mg/animal	50	465/640	5***	365

* The publication contains no information about the doses that were used in the subsequent treatment with the promoter, phorbol myristate acetate.
** 2 Papillomas, 1 sarcoma
*** 3 Papillomas, 2 squamous carcinomas (p = 0.07, statistical test not specified)

According to the investigators, the study demonstrated marginally significant increases in the incidences of squamous carcinoma and papilloma as compared with the phorbol myristate acetate control. No tumour incidence data were reported (Van Duuren et al., 1987).

The available data from carcinogenicity studies of dichloroacetyl chloride do not allow a conclusive evaluation of the chemical's carcinogenic potential on account of the following, and other, points of criticism:

- The publications contained no precise information on dose selection or any indication as to whether the high dose/concentration was in the range of the maximum tolerated dose.
- No precise data were presented on tumour incidences among the historical controls for the chosen strain.

Therefore it is not possible to judge whether the marginally significant increases in tumour incidences were random or substance-related.

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

Arc welding can produce phosgene and other compounds, including dichloroacetyl chloride, when the ambient air contains residual trichloroethylene

or 1,1,1-trichloroethane, which are used for cleaning steel (Dahlberg and Myrin, 1971; Ross, 1985). It was therefore suspected that under these conditions the dichloroacetyl chloride that formed might be responsible for the signs and symptoms noted in 11 workers, which included dry cough, sometimes with spit, shortness of breath, catarrh and throat irritation, eye irritation, an unpleasant taste in the mouth, tightness in the chest and wheezing or rhonchi in the chest. However, no suitable method was available to the investigator for the detection for dichloroacetyl chloride in air. The trichloroethylene and 1,1,1-trichloroethane concentrations were well below the threshold limit values for the United States. No phosgene was detected (Ross, 1985).

Dichloroacetyl chloride air levels of approx. 10 ppm (equivalent to approx. 60 mg/m³) during arc welding produced respiratory tract irritation (Dahlberg and Myrin, 1971).

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 listed dichloroacetyl chloride in the "Yellow Pages" (Substances being Examined for the Establishment of MAK Values and BAT Values") of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie is order that the carcinogenic effect be examined (DFG, 2004).

Table 3. Carcinogenicity study with inhalation exposure of male Sprague-Dawley rats, 30 exposures (6 hours/day, 5 days/week) in dynamic exposure chambers, life-span observation, concentrations analysed by IR spectroscopy at half-hour intervals (Sellakumar et al., 1987)

Exposure in ppm		No. of animals	Nasal lesions observed in the animals							Tumours in other organs			Life-span in days
Nominal	Analytical		Number of animals with			Incidence of nasal tumours				Benign	malignant	Total number	
			Nasal tumours	Rhinitis	Squa-mous meta-plasia	Polyps/ papillo-mas	Squa-mous cell carcino-ma	Other malignant tumours	Total number				
Controls (air)													
0	0	98	0	80	9	0	0	0	0	13	11	24	613
β-Propiolactone – hydrolysis rate ($T_{½}$): 60 minutes, > 95% pure													
5	5	50	33	24	24	11	21	4	36	7	4	11	652
10	10	50	24	26	21	5	20	0	25	0	0	0	352
Dichloroacetyl chloride – hydrolysis rate ($T_{½}$): 0.004 minutes at –20 °C, > 95% pure													
0.5	0.53	50	0	44	8	0	0	0	0	10	2	12	528
1.0	1.03	50	0	44	10	0	0	0	0	6	8	14	524
2.0	2.00	50	2	45	8	1	1	1	3	14	5	19	595
Methyl methanesulphonate – hydrolysis rate ($T_{½}$): 580 minutes, > 95% pure													
50	50.3	80	47	49	5	11	33	4	48	25	3	28	495

Table 4. Carcinogenicity study with inhalation exposure of male Sprague-Dawley rats, 30 exposures (6 hours/day, 5 days/week) in dynamic exposure chambers, observation until spontaneous death (Sellakumar et al., 1987)

Exposure in ppm	No. of animals	Number of malignant tumours in various organs (other than the nose)											
		Lymphoid leukaemia	Fibrosarcoma, subcutaneous	Haemangioendothelial sarcoma	Lymphosarcoma	malignant lymphoma	Squamous cell carcinoma	Adenocarcinoma	Acinar carcinoma	Hepatocellular carcinoma	Solid cell carcinoma, thyroid	Phaeochromocytoma	Total number
Control (air)													
0	98		2		2	4	1 Zymbal gland					2 adrenal gland	11
β-Propiolactone													
5	50	1	1							1 liver	1		4
10	50												0
Dichloroacetyl chloride													
0.5	50					2							2
1.0	50		2			2	2 Zymbal gland 1 skin	1 salivary gland					8
2.0	50			1 liver			1 Zymbal gland 1 skin		1 sebaceous gland			1 adrenal gland	5
Methyl methanesulphonate													
50	80					1		1 adrenal gland 1 salivary gland					3

Table 5. Carcinogenicity study with inhalation exposure of male Sprague-Dawley rats, 30 exposures (6 hours/day, 5 days/week) in dynamic exposure chambers, observation until spontaneous death (Sellakumar et al., 1987)

Exposure in ppm	No. of animals	Number of benign tumours in various organs (other than the nose)								
		Fibroma, subcutaneous	Lipoma, subcutaneous	Adenoma	Fibroadenoma, mammary gland	Leydig cell tumour, testis	Haemangioma, spleen	Polyp	Papilloma	Total number
Control (air)										
0	98	5		3 adrenal gland 2 thyroid gland		3				13
β-Propiolactone										
5	50	3		1 lung 1 islet cells (pancreas)			1	1 larynx		7
10	50									0
Dichloroacetyl chloride										
0.5	50	2	4	2 thyroid gland	2					10
1.0	50	4							2 skin	6
2.0	50	4	3	1 kidney	2				2 skin 2 forestomach	14
Methyl methanesulphonate										
50	80	9	2	1 adrenal gland 1 parathyroid gland 2 thyroid gland 1 islet cells (pancreas) 1 salivary gland	3			2 larynx 2 trachea	1 skin	25

References

Dahlberg, J.A., Myrin, L.M.
The formation of dichloroacetyl chloride and phosgene from trichloroethylene in the atmosphere of welding shops
Ann. Occup. Hyg., 14, 269–274 (1971)

DFG (Deutsche Forschungsgemeinschaft, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)
List of MAK and BAT Values 2004
Wiley-VCH Verlag GmbH, Weinheim (2004)

EC Existing Substances Regulation, Annex 1
Official Journal of the European Communities No. L84 of 05.04.1993

Hoechst AG, Pharma-Forschung/Laboratorium für Gewerbe- und Arzneimitteltoxikologie
Dichloracetylchlorid – Akute orale Toxizität an weiblichen SPF-Wistar-Ratten
Unpublished report No. 106/67 (1967 a)

Hoechst AG, Pharma-Forschung/Laboratorium für Gewerbe- und Arzneimitteltoxikologie
Dichloracetylchlorid
Unpublished report No. 107/67 (1967 b)

Hoechst AG, Pharma Forschung Toxikologie und Pathologie
Dichloracetylchlorid – Prüfung auf Hautreizung am Kaninchen
Unpublished report No. 88.1920 (1988 a)

Hoechst AG, Pharma Research Toxicology and Pathology
Dichloressigsäurechlorid – Study of the mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli
Unpublished report No. 88.0505 (1988 b)

Hoechst AG
DIN safety data sheet Dichloressigsäurechlorid (1990)

Koenig, G., Lohmar, E., Rupprich, N.
Chloroacetic acids
In: Ullmann's encyclopedia of industrial chemistry
5th ed., vol. A6, 537–552
VCH Verlagsgesellschaft mbH, Weinheim (1986)

Lide, D.R., Frederikse, H.P.R. (eds.)
CRC Handbook of chemistry and physics
77th ed., p. 3-10
CRC Press, Boca Raton, New York, London, Tokyo (1996)

Rosca, S., Szövérffy, A., Gábos, A.R., Rosca, G., Tiganescu, D.
Microscopic study of the rat liver after dichloroacetylchloride administration (English abstract of a Hungarian publication)
Rev. Med. (Tirgu-Mures), 28, 151–154 (1982)

Ross, D.S.
Case history, dichloroacetyl chloride exposure?
Occup. Health, 37, 116–118 (1985)

Sellakumar, A.R., Snyder, C.A., Albert, R.E.
Inhalation carcinogenesis of various alkylating agents
J. Natl. Cancer Inst., 79, 285–289 (1987)

Smyth, H.F., jr., Carpenter, C.P., Weil, C.S.
Range-finding toxicity data: list IV
Arch. Ind. Hyg. Occup. Med., 4, 119–122 (1951)

Szövérfi, A.B., Rosca, S., Rosca, G., Hodor, I., Varga, Z., Abrahám, A.
Histological and histochemical aspects produced by dichloroacetyl chloride in the kidneys (English abstract of a Hungarian publication)
Rev. Med. (Tirgu-Mures), 29, 77–81 (1983)

Van Duuren, B.L., Kline, S.A., Melchionne, S., Seidman, I.
Chemical structure and carcinogenicity relationships of some chloroalkene oxides and their parent olefins
Cancer Res., 43, 159–162 (1983)

Van Duuren, B.L., Melchionne, S., Seidman, I.
Carcinogenicity of acylating agents: chronic bioassays in mice and structure-activity relationships (SARC)
J. Am. Coll. Toxicol., 6, 479–487 (1987)

Windholz, M., Budavari, S., Blumetti, R.F., Otterbein, E.S. (eds.)
The Merck index
10th ed., p. 443
Merck & Co., Inc., Rahway, New Jersey (1983)

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K.
Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals
Environ. Mol. Mutagen., 19, Suppl. 21, 2–141 (1992)