

GÜNTER KOENIG, Hoechst Aktiengesellschaft, Augsburg, Germany

ELMAR LOHMAR, Hoechst Aktiengesellschaft, Köln, Germany

NORBERT RUPPRICH, Bundesanstalt für Arbeitsschutz, Dortmund, Germany

MARTIN LISON, CABB GmbH, Sulzbach, Germany

ALEXANDER GNASS, CABB GmbH, Gersthofen, Germany

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1. Introduction

Chloroacetic acid and its sodium salt are the most industrially and economically important of the three chlorination products of acetic acid. The sections on physical and chemical properties, production, quality specifications, uses, and derivatives are reported separately for each of these three acids, whereas those on environmental protection, chemical analysis, containment materials, storage, transportation, and economic aspects are considered together.

2. Chloroacetic Acid

Chlorinated acetic acids have become important intermediates in organic synthesis because of the ease of substitution of the Cl atoms. Chloroacetic

acid [79-11-8] (ClCH_2COOH , M_r 94.50, monochloroacetic acid, chloroethanoic acid) is the most industrially significant [1]. It does not occur in nature and was first discovered as a chlorination product of acetic acid by N. LEBLANC in 1841. It was synthesized in 1857 by R. HOFFMANN, who chlorinated acetic acid by using sunlight to initiate the reaction. Discovery of other reaction accelerators, such as phosphorus, iodine, sulfur, or acetic anhydride, followed rapidly. Development of commercial processes, based mainly on acetic acid chlorination and later on acid hydrolysis of trichloroethylene, followed.

2.1. Physical Properties

Pure chloroacetic acid is a colorless, hygroscopic, crystalline solid, which occurs in

Table 1. Common physical data of chloroacetic acid

Parameter	Form			
	α	β	γ	δ
f_p	62–63 °C	55–56 °C	50–51 °C	43.8 °C
Latent heat of fusion, ΔH_f	19.38 kJ/mol	18.63 kJ/mol	15.87 kJ/mol	–
Density	d_4^{25} 1.3703	(liquid)		
	d_{20}^{20} 1.58	(solid)		
Refractive index	n_D^{20} 1.4297			
Surface tension, σ (100 °C)	35.17 mN/m			
Viscosity, η				
70 °C	2.16 mPa s			
100 °C	1.32 mPa s			
130 °C	1.30 mPa s			
Degree of dissociation in water (potentiometric) (25 °C)	1.52×10^{-3}			
Dielectric constant (100 °C)	16.8			
Electrical conductivity, lowest value measured (70 °C)	3.1 $\mu\text{S}/\text{cm}^*$			
Specific heat capacity, c_p				
Solid, 15–45 °C	144.02 J mol ⁻¹ K ⁻¹			
Liquid, 70 °C	180.45 J mol ⁻¹ K ⁻¹			
Liquid, 130 °C	187.11 J mol ⁻¹ K ⁻¹			
Heat of combustion, ΔH_c	715.9 kJ/mol			
Heat of evaporation, ΔH_v	50.09 kJ/mol			
Heat of formation, ΔH_f (100 °C):	–490.1 kJ/mol			
Heat of sublimation, ΔH_{subl} (25 °C):	88.1 kJ/mol			
Heat of solution in H ₂ O, ΔH_{soln} (16 °C)				
Solid	–14.0 kJ/mol			
Liquid	1.12 kJ/mol			
Flash point (DIN 51 758)	126 °C			
Ignition temperature (DIN 51 794)	460 °C			
Lower explosion limit in air (101.3 kPa)	8 vol%			

*Rises steeply if traces of water present.

monoclinically prismatic structures existing in the α -, β -, γ -, and also possibly the δ -form. The α -form is the most stable and the most important industrially.

Published physical data vary widely [1]. Some of the most common values appear in Tables 1 and 2.

Table 2. Vapor pressure and solubility in water of the α -form of chloroacetic acid

Vapor pressure		Solubility in water		
Temperature, °C	Pressure, kPa	Temperature, °C	g/100 g solution	g/100 g H ₂ O
189	101.3	0	71	245
160	40	10	76	317
150	28	20	80.8	421
140	19	30	85.8	604
130	13	40	90.8	987
100	4.3	50	95	1900
90	2.6	60	99	–
80	1.1			

Chloroacetic acid has excellent solubility in water and good solubility in methanol, acetone, diethyl ether, and ethanol, but is only sparingly soluble in hydrocarbons and chlorinated hydrocarbons. Chloroacetic acid forms azeotropes with a number of organic compounds [2]. The freezing points of various binary mixtures of chloroacetic acids are shown in Figure 1.

2.2. Chemical Properties

The high reactivity of the carboxylic acid group and the ease of substitution of the α -Cl atom are directly related. As a result, chloroacetic acid is a common synthetic organic intermediate, either as the acid itself or as an acid derivative (e.g., salt, ester, anhydride, acyl chloride, amide, hydrazide, etc.). Some important reactions that are used for industrial applications are as follows.

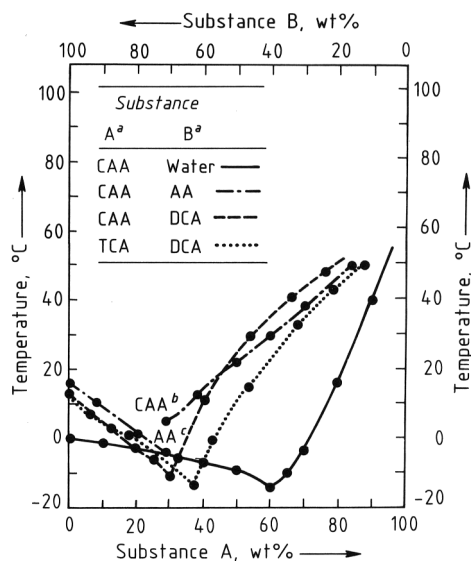


Figure 1. Freezing points of binary mixtures
 a) Acetic acid (AA), chloroacetic acid (CAA), dichloroacetic acid (DCA), trichloroacetic acid (TCA); b) Crystalline phase CAA; c) Crystalline phase AA

Reaction with inorganic bases, oxides, and carbonates or with organic bases gives salts; some salts form adducts with chloroacetic acid. Sodium chloroacetate [3926-62-3] is an important commercial product.

Chloroacetic acid esters are obtained by reaction with alcohols or olefins; methyl chloroacetate [96-34-4], ethyl chloroacetate [105-39-5], and *tert*-butyl chloroacetate [107-59-5] are also important industrially.

Chloroacetyl chloride [79-04-9] is produced from the acid by reaction with POCl_3 , PCl_3 , PCl_5 , thionyl chloride (SOCl_2), phosgene (COCl_2), etc. (see Section 2.6.2).

Chloroacetic acid reacts with chloroacetyl chloride to form bis(chloroacetic)anhydride [541-88-8], which can also be obtained by dehydration of chloroacetic acid with P_2O_5 or by reaction of chloroacetic acid with acetic anhydride. Chloroacetyl chloride forms mixed anhydrides with other carboxylic acids, e.g., acetic chloroacetic anhydride [4015-58-1].

Nucleophilic substitution of the chlorine atom is an important reaction when the product is used as an intermediate in organic syntheses. For example, heating neutral or basic aqueous solutions hydrolyzes the chlorine atom. This is an industrial method of producing glycolic acid

[79-14-1] (hydroxyacetic acid) and diglycolic acid [110-99-6] (2,2'-oxydiacetic acid).

Heating the salts gives glycolide, 1,4-dioxane-2,5-dione [502-97-6]. Reaction with sodium or potassium hydrogen sulfide forms thioglycolic acid [68-11-1] and thiodiglycolic acid [123-93-3].

Reaction with ammonia gives either aminoacetic acid [56-40-6] (glycine) as the main product or, depending on reaction conditions, nitrilotriacetic acid [139-13-9]. If methyl chloroacetate reacts with ammonia at low temperature, chloroacetamide [79-07-2] is obtained. By reaction with tertiary amines in alkaline solution various commercially important betaines are formed (e.g., *N*-lauryl betaine [683-10-3]).

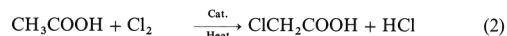
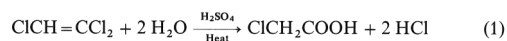
Aromatic compounds, such as naphthalene, undergo electrophilic substitution with chloroacetic acid over suitable catalysts to form arylacetic acids.

Reaction with potassium cyanide in a neutral solution gives the commercially important cyanoacetic acid [372-09-8], which is used as an intermediate in the production of synthetic caffeine [58-08-2]. Reaction with potassium iodide forms iodoacetic acid [64-69-7].

The corresponding phenoxyacetic acids, some of which are of industrial importance, are made by phenol etherification in the presence of sodium hydroxide. Another industrially significant ether formation process gives carboxymethyl derivatives with a relatively high degree of etherification by reacting polysaccharides, such as cellulose, starch, guar, etc., in a strongly alkaline sodium hydroxide medium.

2.3. Production

A multitude of methods have been proposed and patented for the production of chloroacetic acid [1, 3–15]. Historically both the hydrolysis of 1,1,2-trichloroethylene [79-01-6] catalyzed with sulfuric acid (Eq. 1), and the catalyzed chlorination of acetic acid with chlorine (Eq. 2) were used to produce chloroacetic acid on an industrial scale, however, only the latter (and older) process is now used.



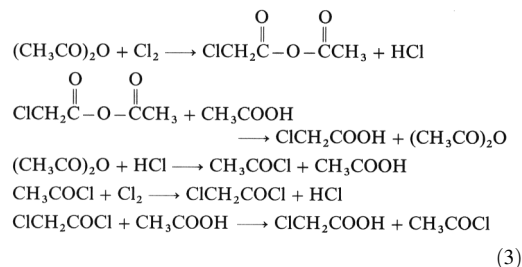
2.3.1. Hydrolysis of Trichloroethylene [13–15]

Equal amounts of trichloroethylene and 75 % sulfuric acid are reacted at 130–140 °C in a continuous process so that with complete trichloroethylene conversion, the resultant reaction mixture contains about 50 % chloroacetic acid and 1–2 % water. This blend is vacuum distilled to give pure chloroacetic acid. During this process the vapors are washed with water, which is returned to the sulfuric acid as a diluent. The resultant hydrogen chloride gas is washed with the fresh trichloroethylene and then purified by freezing and absorbing in water. Trichloroethylene (1500–1850 kg) and H₂SO₄ (600 kg, 95 %) gives 1000 kg of finished product and 700–750 kg of HCl gas as byproduct.

The trichloroethylene method produces highly pure chloroacetic acid free of di- or trichloroacetic acid. The purification procedure consists of separation from trichloroethylene, sulfuric acid, and water. Despite the purity of the chloroacetic acid formed, this method has fallen into disuse because of the high cost of trichloroethylene and the large amount of HCl produced.

2.3.2. Chlorination of Acetic Acid

Synthesis. This method converts acetic acid into chloroacetic acid with high selectivity [1]. This is achieved by using suitable catalysts [13, 16–33]. When acetic anhydride is the catalyst, the reaction mechanism is as follows (Eq. 3) [22]:



Various inhibitors have also been proposed to suppress formation of dichloroacetic acid, which results from chlorination of chloroacetic acid in the crude mixture. This eliminates or

reduces the purification process for technical grades [34–38].

Purification. The high degree of purity required for many products can only be obtained by separating the di- and trichloroacetic acids. Fractional distillation is unsuitable because the boiling points of the three chlorinated acetic acids are so close. Azeotropic distillation [39] and extractive distillation [40, 41] have been suggested for separating dichloroacetic acid; it is doubtful, however, that these methods are used.

An industrially important purification process is *crystallization* without use of a solvent. It is based on the higher melting point of the α -modification of chloroacetic acid. The di- and trichloroacetic acids are removed in the mother liquor.

Crystallization is carried out either in stationary finger crystallizers [42] or in agitated stirrer crystallizers. With the latter, the mother liquor is separated from the crystal slurry after crystallization by using a centrifuge [43, 44]. The product is washed with water or acetic acid and discharged. The chloroacetic acid is usually melted and converted into flakes. In stationary machines, crystallization is carried out by using cold fingers. When all the chloroacetic acid has crystallized, the mother liquor is drained; the pure crystalline product is then melted and flaked.

Another purification method that has been described is a thin-layer crystallization process with the raw material [45]. Use of a water content of 5–25 % without organic solvent is also possible [46].

Solvents have also been used for crystallization. Solvents, such as carbon tetrachloride [44, 47], dichloromethane [48], or hydrocarbons with three chlorine atoms (e.g., trichloroethylene), give crystals that are easy to filter [49].

Common to all of these crystallization methods is obtaining a mother liquor consisting of acetic acid, chloroacetic acid, and di- and trichloroacetic acids. In the most favorable cases, this mixture is further chlorinated to form the industrially useful trichloroacetic acid (see Section 4.3).

Meanwhile, a more important purification method is the catalytic hydrodechlorination of

the undesired byproducts dichloro- and trichloroacetic acid. Di- and trichloroacetic acids in the chlorinated crude acid can be dechlorinated by catalytic hydrogenation at elevated temperature to form chloroacetic acid or acetic acid. Palladium on a carrier, such as carbon or silica gel, is normally employed [50].

When the reaction is carried out in the vapor phase, dichloroacetic acid is dechlorinated primarily to acetic acid [51]. However, when Pd is used on a finely dispersed, inert carrier in the liquid phase at 130–150 °C, dichloroacetic acid is dechlorinated selectively to form chloroacetic acid [52]. Modifications of this procedure, such as spraying the crude acid with hydrogen gas under vacuum [53] or trickling the acid over the catalyst in the fixed bed [54, 55] have also been described.

Selectivity is increased if HCl is mixed with the crude acid before it and the circulating hydrogen contact the catalyst in the fixed bed [56]. Acid chlorides and anhydrides are saponified before dechlorination [57]. A particularly active and selective catalyst is Pd on silica gel (particle size 40–200 μm) [58]. Especially good results are obtained by employing a cocatalytically effective additive, such as sodium acetate [59]. The catalyst can be made more effective by enrichment of the noble metal on its surface [60, 61]. Spent catalyst can be reactivated by treatment

with chlorine [62, 63]. Pd catalysts on optimized active charcoal carriers give lower amounts of over-reduction byproducts (aldehydes, etc.) [64]. For the hydrogenation step a loop reactor can be used [65].

A reduction of dichloroacetic acid from 2000 to 210 ppm can be achieved by treatment of crude chloroacetic acid with nonnoble metal catalysts without hydrogen at temperatures between 100 and 140 °C [66].

An industrial-scale chlorination process is shown in Figure 2. The mixture of acetic acid, acetic anhydride, and recycled acetyl chloride is chlorinated at 90–140 °C in reactor (a) or in several cascade reactors. Only traces of chlorine are still present in the HCl gas formed. Chloroacetic acid, acetic acid, and acetic anhydride are condensed by using water-cooled condensers (b) and then returned to the reactor. Acetyl chloride entrained in the HCl gas is condensed (c) in a subsequent low-temperature process and recycled. The HCl gas is further purified and usually converted into concentrated aqueous hydrochloric acid.

The crude acetic acids can be vacuum distilled (d) before the hydrogenation step but this purification step is not obligatory. Di- and trichloroacetic acids in the crude distilled material are dechlorinated (f) to chloroacetic acid at 120–150 °C, using a palladium catalyst and a

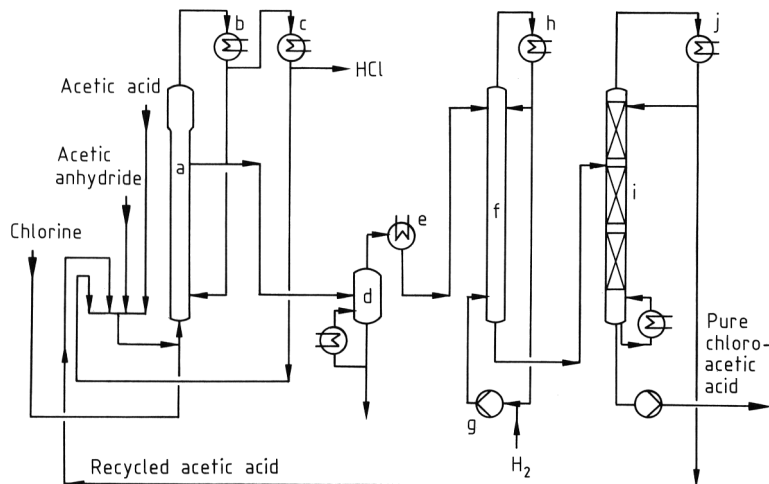


Figure 2. Chloroacetic acid obtained by the chlorination–hydrogenation process
 a) Chlorinating reactor; b) Condenser for acetic acid, acetic anhydride, chloroacetic acid; c) Condenser for acetyl chloride; d) Evaporator; e) Condenser for chloroacetic acid; f) Hydrogenation reactor; g) Hydrogen compressor; h) Condenser; i) Distillation column; j) Condenser for acetic acid

large excess of hydrogen. Acetic acid is taken overhead from the vacuum fractionation column (i); the bottom product is pure chloroacetic acid. Optionally, the chloroacetic acid can be further purified by distillation to remove high-boiling impurities like condensation products of aldehydes formed in the hydrogenation step.

A total of 660–780 kg of acetic acid and 780–1020 kg of chlorine are required per 1000 kg of pure acid, depending on the method used (in crystallization processes, the mother liquors are regarded as lost). The process also gives 400–420 kg of HCl.

2.4. Quality Specifications

Chloroacetic acid is usually marketed to the following specifications:

- Chloroacetic acid: min. 99.0 wt %,
- Dichloroacetic acid: max. 0.2 wt %,
- Acetic acid: max. 0.2 wt %,
- Water: max. 0.2 wt %,
- Iron: max. 5 mg/kg,
- Lead: max. 1 mg/kg.

Specially purified grades of chloroacetic acid are marketed with max. 0.05 % or even max. 0.03 % dichloroacetic acid. Technical grades contain up to 2 % dichloroacetic acid.

2.5. Uses

Most of the chloroacetic acid produced is used to manufacture several hundred thousand tons annually of carboxymethyl cellulose [9004-32-4], CMC (→ Cellulose Ethers). Starch can be reacted with chloroacetic acid to give carboxymethyl starch, which is as widely used as CMC (→ Starch). Other polysaccharides modified with chloroacetic acid are less important.

Another major application is the production of herbicides based on arylhydroxyacetic acids (→ Chlorophenoxyalkanoic Acids). These herbicides are some of the most widely used. Chloroacetic acid and methyl chloroacetate are also employed for making the insecticide dimethoate and the herbicides benazoline and methyl β -naphthylxyacetate.

A third important outlet for chloroacetic acid is the manufacture of thioglycolic acid (mercaptoacetic acid [68-11-1]), obtained from reaction of chloroacetic acid with sodium or potassium hydrogen sulfide or other sulfur compounds (→ Mercaptoacetic Acid). It is used as its salt, ester, or another derivative. The largest amount is employed to produce stabilizers for poly(vinyl chloride). Moreover, thioglycolic acid and its esters are used in hair cosmetics (→ Hair Preparations).

Another important industrial application is the production of long-chain betaines like *N*-lauryl betaine [683-10-3] that are used as surfactants for cleaners or personal care products.

A minor use of chloroacetic acid is in the production of glycolic acid by saponification with an alkali hydroxide. Glycolic acid is used as an auxiliary in textile printing, leather treating, furs finishing, as a component for cleaners and as a peeling agent for skin surface treatment (“alpha-hydroxy acids” [67]); the butyl ester is employed as a paint additive (Polysolvan O), and glycolic acid esters acylated with *o*-phthalic acid half-esters are used as plasticizers (→ Plasticizers).

Apart from the major fields of application mentioned above, chloroacetic acid and its derivatives are used in a multitude of other organic synthetic reactions. For example, caffeine and barbiturates, which are important hypnotics, can be made from cyanoacetic acid or its esters. Chloroacetic acid condenses with aromatic hydrocarbons to form arylacetic acids. Reaction with naphthalene gives 1-naphthylacetic acid as the main product and 2-naphthylacetic acid as the byproduct. Both substances promote plant growth. Chloroacetic acid also is important in the syntheses of coumarin and vitamin B₆ (→ Vitamins).

2.6. Derivatives

2.6.1. Sodium Chloroacetate

Physical, Chemical Properties. The sodium salt ClCH₂COONa [3926-62-3], *M_r* 116.5, is of particular importance. It is colorless and slightly hygroscopic, and has good storage stability. It dissolves readily in water (44 wt % at 20 °C), giving a neutral solution. It has limited solubility

in other polar solvents and is insoluble in nonpolar solvents. It hydrolyzes in water, depending on temperature and time, forming glycolic acid and sodium chloride.

Production. This salt is manufactured by reacting sodium carbonate with chloroacetic acid in batches or in a continuous process [68, 69].

In exceptional cases, localized superheating (about 150 °C) may occur during the reaction. If it does, slow thermal decomposition can take place, producing sodium chloride and polyglycolide as the main products with pronounced evolution of gas.

Another method of manufacturing sodium chloroacetate is spraying molten chloroacetic acid together with 50% caustic soda solution into a spray drier [70].

The production of salts of chloroacetic acids in fluidized beds has been described [71].

Uses. The uses for sodium chloroacetate are virtually the same as those for its free acid. The amount of salt required is less and depends on whether the free chloroacetic acid is used as an 80% aqueous solution or as a melt.

2.6.2. Chloroacetyl Chloride

Physical Properties. Chloroacetyl chloride [79-04-9], ClCH_2COCl , M_r 112.95, is a colorless, highly corrosive liquid that has a pungent odor and fumes when exposed to moist air; bp 105 °C (101.3 kPa), d_4^{20} 1.42, n_D^{20} 1.454.

Production. Chloroacetyl chloride is usually manufactured from chloroacetic acid by reaction with phosphorus trichloride, thionyl chloride, sulfuryl chloride, or phosgene. It is also obtained by chlorination of acetyl chloride in the presence of stronger aliphatic acids, preferably chloroacetic acids, or from sodium chloroacetate and the usual chlorinating agents.

One patent describes the manufacture of chloroacetyl chloride by chlorination of a mixture of 5–50 wt% acetyl chloride in acetic anhydride at 70–100 °C [72]. Another claims reaction of chloroacetic acid and trichloroethylene in the presence of iron(III) chloride and hydrochloric acid at 150 °C and 2 MPa [72]. Chloroacetyl

chloride also has been obtained in 97.1% yield and with a purity of 99.8% by reacting chloroacetic acid with phosgene in the presence of palladium chloride at 110 °C [74]. Chlorination of ketene, which must be present in an excess of at least 50%, at 100–200 °C gives chloroacetyl chloride with less than 7% dichloroacetyl chloride [75]. Chloroacetyl chloride can also be made from 1,2-dichloroethylene and oxygen by using catalysts, such as bromine.

Uses. Chloroacetyl chloride is used for many syntheses, e.g., to make adrenaline, chloroacetic acid esters, and the anhydride.

2.6.3. Chloroacetic Acid Esters

Physical Properties. The methyl ester [96-34-4], $\text{ClCH}_2\text{COOCH}_3$, M_r 108.53, is of particular importance. It is a colorless liquid with a pungent odor, bp 128.5–131.5 °C (101.3 kPa), fp –32.7 °C, d^{20} 1.236, soluble in alcohol and ether, and only sparingly soluble in water.

Also important is the ethyl ester [105-39-5], $\text{ClCH}_2\text{COOCH}_2\text{CH}_3$, M_r 122.55, bp 142–144 °C (101.3 kPa), fp –26.0 °C, d^{20} 1.159, nearly insoluble in water, and readily soluble in alcohol and ether.

Of minor industrial importance is the *tert*-butyl ester [107-59-5], $\text{ClCH}_2\text{COOC}(\text{CH}_3)_3$, M_r 150.60, bp 157.5 °C (101.3 kPa), d^{20} 1.4259.

Production. The methyl and ethyl ester can be manufactured from chloroacetic acid and either methanol or ethanol. In another method, trichloroethylene is converted into ethyl 1,2-dichlorovinyl ether, which can be readily hydrolyzed to form chloroacetic acid ethyl ester. The *tert*-butyl ester can be manufactured from chloroacetic acid and isobutylene under pressure (3–12 bar) and elevated temperature (80–110 °C) [76].

Uses. The reactivity of the ester, which is greater than that of the free acid, makes it suitable for many syntheses, e.g., sarcosine, chloroacetamide, thioglycolic acid ester [77] for pharmaceuticals (vitamin A), and crop protection agents (dimethoate). Condensation with aldehydes and ketones gives glycide esters [78]. Other uses are the synthesis of

heterocyclic compounds, e.g., 2-phenylimino-4-oxooxazolidine from the ester and phenyl urea [79], and the well-known condensation of chloroacetic acid and its esters with thioureas to form pseudothiohydantoins.

2.6.4. Chloroacetamide

Physical Properties. Chloroacetamide [79-07-2], $\text{ClCH}_2\text{CONH}_2$, M_r 93.52, colorless crystalline needles, bp 224 °C (101.3 kPa), fp 121 °C, is soluble in water and alcohol, and sparingly soluble in all nonpolar solvents.

Production. Chloroacetamide is obtained on an industrial scale by reaction of methylchloroacetate with ammonia at low temperature [80]. Manufacture from chloroacetic acid and cyanamide at 150–200 °C also has been described [81].

Uses. Chloroacetamide is a versatile intermediate. In addition, it has biocidal properties and, therefore, is used as an industrial preservative. Because of its good solubility in water, chloroacetamide is a particularly suitable biocide for protection of the aqueous phase, e.g., in drilling fluids [82], in water-containing paints [83], and as a wood preservative [84]. Its insecticidal action on aphids [85] and its use as a hardener for urea and melamine resins [86] have also been described.

Various derivatives have the same biocidal effect as chloroacetamide. For instance, *N*-octadecylchloroacetamide is used as an antimicrobial plasticizer [87].

3. Dichloroacetic Acid

3.1. Physical Properties

Dichloroacetic acid [79-43-6], 2,2-dichloroethanoic acid, Cl_2CHCOOH , M_r 128.95, bp 192 °C (101.3 kPa), 102 °C (2.7 kPa), fp 13.5 °C, d_4^{20} 1.564, n_D^{20} 1.466, vapor pressure 0.19 kPa (at 20 °C), dissociation constant 5×10^{-2} mol/L (at 18 °C), is a colorless, highly corrosive liquid that gives off acidic vapors, which irritate the mucous membranes. It is miscible with water in any proportion. Dichloroacetic acid is readily soluble

in the usual organic solvents, such as alcohols, ketones, hydrocarbons, and chlorinated hydrocarbons.

3.2. Chemical Properties

The two chlorine atoms of dichloroacetic acid are susceptible to displacement. For instance, with aromatic compounds, diaryl acetic acids are formed, and with phenol, diphenoxy acetic acids are the products. However, dichloroacetic acid is less prone to hydrolysis than chloroacetic acid. In the manufacture of CMCs and starches, the dichloroacetic acid impurity in the chloroacetic acid gives rise to cross-linking, which is either desirable or undesirable, depending on the use of the end product.

3.3. Production

The most cost-effective production method is the hydrolysis of dichloroacetyl chloride (see Section 3.6.1). Moreover, 98 % dichloroacetic acid can be obtained in 90 % yield by hydrolysis of pentachloroethane with 88–99 % sulfuric acid [88] or by oxidation of 1,1-dichloroacetone with nitric acid and air [89]. Extremely pure dichloroacetic acid can be produced by hydrolysis of the methyl ester [90], which is readily available by esterification of crude dichloroacetic acid. Furthermore, dichloroacetic acid and ethyl dichloroacetate can be obtained by catalytic dechlorination of trichloroacetic acid or ethyl trichloroacetate with hydrogen over a palladium catalyst [91].

Separation of pure dichloroacetic acid from the other chloroacetic acids cannot be carried out by physical methods, especially fractional distillation, because the differences in boiling points, particularly between di- and trichloroacetic acid, are too small. The ester mixtures, on the other hand, can be satisfactorily fractionated in efficient distillation columns. In addition, mixtures of the salts of the three chloroacetic acids can be washed with water, alcohol, or water–alcohol solutions. The dichloroacetate can be dissolved preferentially and acidified to give pure dichloroacetic acid.

Dichloroacetic acid can be produced in the laboratory by reacting chloral hydrate and potas-

Table 3. Technical data of dichloroacetic acid marketed by CABB

Content	Technical grade	Pharma grade
Dichloroacetic acid	min. 98.0%	min. 99.0%
Chloroacetic acid	max. 0.2%	max. 0.2%
Trichloroacetic acid	max. 0.9%	max. 0.9%
Water	max. 0.3%	max. 0.05%
<i>fp</i>	min. 12°C	min. 12°C
Chloral hydrate		100 ppm
Platinum-cobalt scale (Hazen, APHA number)		max. 50

sium or sodium cyanide (Eq. 4).



3.4. Quality Specifications

Dichloroacetic acid is a colorless liquid that is marketed, for instance, by CABB. Table 3 gives the technical data.

3.5. Uses

Dichloroacetic acid is used as a test reagent for analytical measurements during fiber manufacture [poly(ethylene terephthalate)] and as a medicinal disinfectant (substitute for formalin).

Dichloroacetic acid is also used as a deblocking agent in the solid-phase synthesis of oligonucleotides. For this application a dichloroacetic acid is required that is substantially free of chloral (trichloroacetaldehyde) [92, 93].

Dichloroacetic acid, particularly in the form of its esters, is an important intermediate in organic synthesis. It is a reactive starting material for the production of glyoxylic acid, dialkoxy and diaroxy acids, and sulfonamides.

3.6. Derivatives

3.6.1. Dichloroacetyl Chloride

Physical Properties. Dichloroacetyl chloride [79-36-7], Cl_2CHCOCl , M_r 147.40, is a colorless liquid, which has an unpleasant odor and fumes when exposed to moist air; *bp* 106–108 °C (101.3 kPa), d_4^{16} 1.5315, n_D^{16} 1.4638, vapor pressure 3.06 kPa (at 20 °C).

Chemical Properties. Dichloroacetyl chloride undergoes not only reactions typical of acid chlorides, but also displacement reactions of the chlorine atoms in the 2-position. The chemistry of dichloroacetyl chloride and its derivatives is analogous in certain respects to that of glyoxylic acid. Thus, dichloroacetyl chloride reacts with ammonia and amines to form amino acids, with alcohols to form ester acetals and acetals, with benzene to form diarylacetic acids, and with phenols to form diphenoxyacetic acids.

Production. Dichloroacetyl chloride is produced by the oxidation of trichloroethylene. Oxidation with oxygen to form a mixture of dichloroacetyl chloride and chloral has been known since the early 1900s [94]. Patents published in the 1960s describe methods to manufacture dichloroacetyl chloride of > 98 % purity, e.g., at 65–200 °C and 0.2–2 MPa in the presence of free-radical initiators [95], using catalytic quantities of azo compounds and amines [96], and initiating oxidation with UV light and only adding organic nitrogen bases in quantities of 0.005–0.05 % once oxidation has begun [97]. Correspondingly, chloroacetyl chloride and trichloroacetyl chloride can be produced from 1,2-di- and tetrachloroethylene, but these methods are of little industrial significance because the products can be obtained more easily by other processes.

Furthermore, dichloroacetyl chloride is manufactured from pentachloroethane and fuming sulfuric acid or from chloroform and carbon dioxide in the presence of aluminum chloride at high pressure [98]. It has also been produced from ketene and chlorine in the presence of sulfur dioxide [99].

Uses. Dichloroacetyl chloride is used to manufacture dichloroacetic acid (see Section 3.3). In addition, it can be employed for the production of esters and anhydrides. It is used as the starting material to manufacture pharmaceuticals, such as sulfonamides and antibiotics (chloramphenicol), and to produce crop protection agents (e.g., benoxacor).

3.6.2. Dichloroacetic Acid Esters

Physical Properties. Methyl dichloroacetate [116-54-1], $\text{Cl}_2\text{CHCOOCH}_3$, M_r 142.98,

bp 143.3 °C (101.3 kPa), d_4^{20} 1.3808, n_D^{20} 1.4428.

Ethyl dichloroacetate [535-15-9], $\text{Cl}_2\text{CHCOOCH}_2\text{CH}_3$, M_r 157.00, *bp* 158.5 °C (101.3 kPa), d_4^{20} 1.2821, n_D^{20} 1.4386.

Chemical Properties. These esters are highly reactive and, for example, condense with aldehydes and ketones in the presence of dilute metal amalgams to form α -chloro- β -oxyacid esters, which can be converted into the corresponding aldehydes via glycide esters [100]. Dichloroacetic acid esters are readily saponified by boiling water.

Production. These esters are obtained by the usual esterification methods. The methyl and ethyl esters are best produced by alcoholysis of dichloroacetyl chloride.

Uses. These esters are employed as intermediates in the manufacture of chloramphenicol (\rightarrow Antibiotics), dichloroacetamide, and crop protection agents, and are employed as paint resin solvents. The glyceryl and ethylene glycol esters also serve as plasticizers for cellulose derivatives.

4. Trichloroacetic Acid

4.1. Physical Properties

Pure trichloroacetic acid [76-03-9] forms hygroscopic, rhombohedral crystals that are extremely soluble in water and soluble in many organic solvents; Cl_3CCOOH , M_r 163.40, *bp* 197.6 °C (101.3 kPa), *bp* ca. 107 °C (2.8 kPa), *fp* 59.2 °C, d_4^{60} 1.630, n_D^{65} 1.459.

4.2. Chemical Properties

The complete substitution of the hydrogen atoms on the methyl radical by chlorine makes trichloroacetic acid a strong acid ($K = 2 \times 10^{-1}$ mol/L); it also makes the chlorine atoms less prone to substitution than those of chloroacetic acid and dichloroacetic acid. Trichloroacetic acid decomposes to chloroform and carbon dioxide when its aqueous solution is exposed to heat. The decomposition is particularly fast

in the presence of organic or inorganic bases. When water is absent, aniline, resorcinol, and activated carbon can catalyze the decomposition. Purely thermal decomposition takes place only when the boiling point has been exceeded, resulting in the formation of chlorinated hydrocarbons, carbon monoxide and dioxide, and phosgene. Trichloroacetic acid salts with inorganic and many organic bases are known. They decompose when heated in the presence of water to form chloroform.

4.3. Production

Trichloroacetic acid is produced on an industrial scale by chlorination of acetic acid, chloroacetic acid, or chloroacetic acid mother liquors at 140–160 °C [101]. If necessary, calcium hypochlorite is added as a chlorination accelerator [102]. There are conflicting views concerning adding heavy metal salts as chlorination catalysts. Examples of catalysts that have been used are iron and copper compounds, which are precipitated with sulfuric acid or phosphoric acid if decomposition of the reaction mixture occurs [103]; 2 % phosphoric acid [104]; and catalysts and UV light [105]. Trichloroacetic acid has also been produced without catalysts [106, 107].

The crude product, containing about 95 % trichloroacetic acid, is best isolated by crystallizing the melt, removing the mother liquor with most of its impurities, and increasing the purity by centrifugation or recrystallization.

If sulfuric acid is used as catalyst at reaction temperatures of up to 180 °C no further purification is needed.

4.4. Quality Specifications

Trichloroacetic acid is marketed in various degrees of purity. The specifications in Table 4 are typical.

4.5. Uses

Until the 1990s the main application for trichloroacetic acid was the production of its sodium salt, which can be used as a selective herbicide and in formulations with 2,4-D and

Table 4. Typical quality specifications of trichloroacetic acid

Property	Grade		
	Industrial ^a	Ph. Eur. ^b	ACS ^c
Freezing point, min., °C	56	–	–
Trichloroacetic acid, % min.	98.0	98.0	99.0
Dichloroacetic acid, % max.	1.2	–	–
Sulfuric acid, % max.	0.3	–	0.02
Sulfated ash, % max.	–	0.1	–
Water, % max.	0.5	–	–
Heavy metals in the form of:			
Lead, ppm max.	–	–	20
Iron, ppm max.	10	–	10
Phosphate, ppm max.	–	–	5
Chloride, ppm max.	–	100	20
Nitrate, ppm max.	–	–	20
Insoluble matter, % max.	–	–	0.01
Residue after ignition, % max.	–	–	0.03

^aSpecifications of CABB.^bEuropean Pharmacopeia [108].^cSpecifications of ACS [109].

2,4,5-T preparations as a total herbicide. This application is of minor importance now due to the ecotoxicological properties of sodium trichloroacetate (see Section 4.6.3).

Trichloroacetic acid also is employed as an etching or pickling agent in the surface treatment of metals, as a swelling agent and solvent in the plastics industry, as an albumin precipitating agent in medicine, as an auxiliary in textile finishing, and as an additive to improve high-pressure properties in mineral lubricating oils. Because it is strongly corrosive, trichloroacetic acid is used to remove warts and hard skin and to treat various skin afflictions [110, 111]. Trichloroacetic acid and particularly its esters are important starting materials in organic syntheses. The acid undergoes numerous color reactions that can serve to identify a wide range of organic compounds [112].

4.6. Derivatives

4.6.1. Trichloroacetyl Chloride

Physical Properties. Trichloroacetyl chloride [76-02-8], Cl_3CCOCl , M_r 197.9, bp 118 °C (101.3 kPa), d_4^{20} 1.620, n_D^{20} 1.4695, is similar to dichloroacetyl chloride.

Chemical Properties. The acid chloride can be hydrolyzed at 75–85 °C with water to form the

free acid and hydrolyzed with ammonium hydroxide or concentrated sodium carbonate solution to form the salts.

Production. The acetyl chloride is prepared from trichloroacetic acid and various inorganic acid chlorides (e.g., SOCl_2 , PCl_3) or with P_2O_5 and HCl . More useful methods are the oxidation of tetrachloroethylene with fuming sulfuric acid, oxygen, or fuming nitric acid and sulfuric acid at 18–20 °C [113], or from the reaction of pentachloroethane and dry oxygen under UV light [114]. Trichloroacetyl chloride has been obtained in 37 % yield from carbon tetrachloride and carbon monoxide in the presence of aluminum chloride at 200 °C and high pressure [115]. Trichloroacetyl chloride can be produced by chlorination of dichloroacetyl chloride in the presence of pyridine [116].

The most common production method is the gas-phase, photochemical oxidation of tetrachloroethylene with oxygen. The reaction is initiated with UV light, with radioactive irradiation, or it is sensitized with chlorine or iodine [117].

Uses. Trichloroacetyl chloride can be used for the manufacture of the esters and the anhydrides of trichloroacetic acid. It is an important intermediate in the production of pesticides (Chlorpyrifos). It can also be used as a starting material in the production of trifluoroacetic acid [118].

4.6.2. Trichloroacetic Acid Esters

Only the methyl and ethyl esters are of industrial interest. They can be used as solvents, if necessary, and for the production of the amide and polyalcohol esters, which have been suggested for use as plasticizers. Ethyl trichloroacetate is widely used as a co-catalyst in Ziegler-type polymerizations [119].

Methyl trichloroacetate [598-99-2], $\text{Cl}_3\text{CCOOCH}_3$, M_r 177.43, bp 153 °C (101.3 kPa), d_4^{20} 1.4864, n_D^{20} 1.4572.

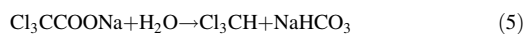
Ethyl trichloroacetate [515-84-4], $\text{Cl}_3\text{CCOOCH}_2\text{CH}_3$, M_r 191.45, bp 167.5 °C (101.3 kPa), d_4^{20} 1.3823, n_D^{20} 1.4505.

4.6.3. Trichloroacetic Acid Salts

The sodium salt is the only one of industrial importance.

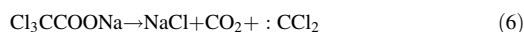
Physical Properties. Sodium trichloroacetate [650-51-1] (TCA, sodium TCA, STCA, NaTA, Cl_3CCOONa , M_r 185.40), is a colorless salt that decomposes at temperatures below the melting point. The salt is very soluble in water and methanol and soluble in polar solvents. The solubility in water at -5°C is 50 wt %, at 20°C 60 wt %, and at 40°C 70 wt %.

Chemical Properties. The salt is stable in the dry state and at normal storage temperature. Hydrolytic cleavage takes place in aqueous solution (Eq. 5).



At the boiling point, this reaction takes place quantitatively within an hour and is used for quantitative analysis of sodium trichloroacetate [120]. At 20 – 25°C the aqueous solution is relatively stable; with a 50 % solution only ca. 1 % is hydrolyzed in 4–6 weeks.

In aprotic solvents, such as 1,2-dimethoxyethane, the reactive intermediate dichlorocarbene is formed as the primary product at elevated temperature (ca. 80°C) (Eq. 6) [121].



When phase-transfer catalysis is used, the dichlorocarbene can add, for example, across olefinic double bonds to give dichlorocyclopropane derivatives [121]. If dichlorocarbene is formed in the absence of other acceptors, it reacts with additional sodium trichloroacetate (Eq. 7).



Consequently, the main products formed during the thermal decomposition of sodium trichloroacetate (combination of Eqs. 6 and 7) were sodium chloride, trichloroacetyl chloride, carbon monoxide, and carbon dioxide; also observed were chloroform, carbon tetrachloride, and traces of phosgene [122].

Thermal decomposition is exothermic (42 kJ/mol) and starts between 125 and 170°C . This decomposition reaction is quenched by adding water; hydrolysis then takes place.

Production. Sodium trichloroacetate is produced industrially by neutralizing trichloroacetic acid with sodium hydroxide solution or sodium carbonate [123, 124].

Uses. Sodium trichloroacetate, together with reducing agents and traces of heavy-metal salts, is recommended as a polymerization catalyst for vinyl compounds [125]. It is useful as a dyeing auxiliary because of the formation of NaHCO_3 during hydrolysis [126]. It also improves absorption of disperse dye systems on polyester (\rightarrow Fibers, 5. Polyester Fibers) and cellulosic fibers [127]. Moreover, in diazo papers developed by heat, sodium trichloroacetate is used to liberate base at 100 – 200°C [128].

Until the 1990s the most important application was the use as a selective herbicide to control monocotyledonous annual or perennial weeds [129–131]. As a soil-applied herbicide its half-life is 1–2 months [132]. For use as a crop protection agent, a minimum content of 95 % sodium trichloroacetate is required. Because the salt in powder form causes severe irritation, the product is usually marketed as granules [133]. Because of its ecotoxicological properties the use of sodium trichloroacetate as a herbicide is meanwhile prohibited in most regions (USA, Canada, European Community, South America except Argentina) but it is still used in less regulated regions like Asia.

5. Environmental Protection

The waste gases formed during chlorination of acetic acid depend on the degree of chlorination. When purification is done by fractional crystallization, less than 1 % of unreacted acetic acid is necessary in the crude acid. In this case chlorine occurs in these waste gases; recovery of the chlorine has been described [134].

Formation of chlorinated hydrocarbon impurities also depends on the production method used. They form as a result of decarboxylation and occur particularly in the manufacture of trichloroacetic acid.

In modern chloroacetic and trichloroacetic acid production plants the waste gases from chlorination steps containing hydrogen chloride, excess chlorine, and organic impurities

are incinerated to produce pure hydrochloric acid.

In the manufacture of dichloroacetic acid by catalytic oxidation of trichloroethylene, residues of the starting materials are always present in the waste gases. Such waste gases are purified by adsorption onto activated charcoal or are incinerated.

Whereas chloroacetic acid and dichloroacetic acid are readily biodegradable by activated sludge floc, only slow biodegradation is observed in the case of trichloroacetic acid even with activated sludge from industrial wastewater treatment plants that is adapted to chlorinated compounds. Chlorinated acetic acids can cause serious interference particularly in community wastewater treatment plants that have not been bioprepared. Preventing effluent contaminated with products of acetic acid chlorination from draining into public sewer systems is therefore essential.

Among the aquatic organisms, algae are the most sensitive species, the half maximal effective concentration (EC_{50}) value of chloroacetic acid is < 1 mg/L [135] towards *Desmodesmus subspicatus*.

Spills of chlorinated acetic acids and their derivatives, resulting, for instance, from transport accidents, should be contained with inert materials (sand or earth) and collected for safe disposal, or neutralized with agents, such as Na_2CO_3 or $NaHCO_3$. Any contaminated soil must be removed (the chlorinated acetic acids are strong pollutants to groundwater). Waste material should be taken to an approved disposal facility (incinerator or wastewater treatment plant).

Chloroacetic acid is flammable at higher temperatures and forms explosive mixtures with air (lower explosion limit 8 vol %). The two other acids are nonflammable. If the acids are involved in a fire, the decomposition gases of trichloroacetic acid and dichloroacetic acid may contain phosgene.

6. Chemical Analysis

Rapid analysis of the purity of mono-, di-, and trichloroacetic acid is adequately provided by determining the melting and freezing points, particularly when the melting depression is caused by known contamination.

Quantitative analysis of chloroacetic acid should include total acidity and a separate determination of dichloroacetic acid, sulfuric acid, hydrochloric acid, water, and heavy metals, as well as total chlorine content by approved methods. From these determinations acetic acid and chloroacetic acid content can be calculated.

Dichloroacetic acid can be determined with a high degree of accuracy by saponification with strong base and subsequent manganometric titration. Dichloroacetic acid values are exaggerated in the presence of trichloroacetic acid. If trichloroacetic acid is present, preliminary saponification with dilute base is advisable.

Acetic acid and dichloroacetic acid can be directly separated and quantitatively determined by gas chromatography. In addition to these two acids, trichloroacetic acid can also be detected in the form of its methyl ester by gas chromatography. Dichloroacetic acid and acetic acid in the presence of chloroacetic acid can also be determined accurately by HPLC [136]. This method is not recommended for chloroacetic acid itself because titration to determine total chlorine content is more accurate.

Trichloroacetic acid is determined by hydrolysis in acid solution to chloroform and quantitative determination of the hydrogen ions needed for saponification. Formation of a deep-red complex from pyridine and chloroform can be used for a colorimetric method [137]. Nitron [1,4-diphenyl-3-(phenylamino)-1*H*-1,2,4-triazolium hydroxide] produces a salt with trichloroacetic acid, which is suitable for detecting the acid [138].

Dichloroacetic acid can be determined by polarography in mixtures with trichloroacetic acid [139]. Large amounts of chloroacetic acid interfere with the determination.

Determination of heavy metals in all chlorinated acetic acids and derivatives is carried out by familiar methods, such as atomic absorption or colorimetry. For lead, inverse voltammetry is also used.

7. Containment Materials, Storage, and Transportation

Because of the corrosiveness of these chemicals, most metals are unsuitable for use as container materials. Thus, chlorination is carried out in

ceramic-lined, lead-coated steel containers or in glass-lined vessels. Pipelines are made of glass-lined steel or steel lined with polytetrafluoroethylene (PTFE) or perfluoroalkoxy (PFA) polymers (e.g., tetrafluoroethylene). Silver that has been rendered inert by a silver chloride layer can be used for parts of the equipment (e.g., valves, heat exchangers, distillation column linings, stirrers). Tantalum and titanium (with certain temperature limits) are other suitable metallic materials. Carbon (Dia-bon) and glass are effective materials for heat exchangers. In addition to PTFE and PFA/TFA, fluorinated ethylene-propylene copolymers (FEP), poly(vinyl chloride) (PVC), polyethylene, and polypropylene can be used at relatively low temperature and for aqueous solutions.

The aqueous solution can be handled in special stainless steel or rubber-lined steel containers at temperatures below 40 °C. Iron with a baked phenolic resin coating can be used below 100 °C.

During storage and transportation, high corrosivity and, with chloroacetic acid, toxicity must also be considered. Chlorinated acetic acids and their derivatives are classified as dangerous substances. They are subject to nearly all national and international handling regulations. Containers must be labeled in the stipulated manner. In the case of chloroacetic acid, the most important forms that are shipped are the melt (in glass-lined railroad cars or titanium-lined tank trucks) and the 80 % aqueous solution (in stainless steel or rubber-lined tank trucks and containers).

Crystallized, flaked chloroacetic acid and trichloroacetic acid are obtained by utilizing chilled rolling flakers and, more recently, with chilled conveyor-type flakers; the coarser flakes manufactured in this manner tend to agglomerate less and, therefore, are preferred. Flakes are packed in multilayer paper sacks or in polyethylene bags contained in fiberboard or iron drums. Small quantities are supplied in polyethylene containers or in glass bottles. Dichloroacetic acid and most of its liquid derivatives usually are shipped in iron drums with polyethylene inner containers.

If stored in a cool, dry place, the chlorinated acetic acids and their derivatives are stable almost indefinitely, although the crystallized products have a marked tendency to agglomerate.

8. Economic Aspects

The worldwide consumption of monochloroacetic acid in 2006 was estimated at 420 000 t/a, divided as follows: Europe ≈36.6 %, China ≈43.2 %, India ≈7.6 %, Japan ≈6.2 %, and America ca. 6.4 %

Recognized manufacturers are AKZO Nobel, CABB, and Dow.

Accurate figures are not available on the amounts of chloroacetic acid and its derivatives used for different applications. However, by far the largest amount goes into the production of CMC, starch, and polysaccharides derivatives. This is followed by herbicides based on phenox-yacetic acids (2,4-D, MCPA, 2,4,5-T), surfac-tants, and thioglycolic acid (used in stabilizers for PVC and in hair preparations). All other applica-tions account for about 17 % of annual production.

Dichloroacetic acid is of little economic im-portance. More significant are its acid chloride and methyl ester, which are used as intermediates in the manufacture of agrochemicals (benoxacor) and chloramphenicol.

In the case of trichloroacetic acid, the sodium salt was very important until the 1990s. About 21 000–23 000 t/a were used worldwide as a selective herbicide. Meanwhile, only some 100 t/a are consumed in South America whereas the market in India, China and other Asian countries is not known.

9. Toxicology and Occupational Health

Chloroacetic Acid and Chloroacetate. Chloroacetic acid is a corrosive solid material. The lowest published median lethal dose (LD₅₀) is 76 mg/kg for oral administration to rats [140]. Single oral administration of lethal doses resulted in apathy and loss of body mass. Death occurred several days after administra-tion [141].

Acute inhalational exposure of rats led to eye and pulmonary irritation. The irritation threshold is 23.7 mg/m³. The LC₅₀ is 180 mg/m³ [142].

Prolonged inhalation of chloroacetic acid resulted in reduced body mass, reduced oxygen consumption, hemoglobinemia, and inflamma-

tion of the respiratory tract. A threshold limit value for chloroacetic acid of 1 mg/m^3 is recommended if these experimental animal findings are taken as a basis [142]. Until now, the American Conference of Governmental Industrial Hygienists (ACGIH) has not established a threshold limit value (TLV) but some countries in Europe, e.g., Germany, the TLV (short-term and long-term) = 1 ppm (4 mg/m^3) [143].

Repeated intake of 0.1% chloroacetate in the diet led to depressed growth curves and an increased level of liver glycogen [144]. A major metabolic pathway for chloroacetic acid is reaction with glutathion, finally yielding thiodiacetic acid [145]. One report has shown that chloroacetic acid elevates mutant rates in the mouse lymphoma forward mutation assay [146].

Dichloroacetic Acid and Dichloroacetate.

Dichloroacetic acid, a clear colorless liquid, is corrosive to the skin and mucous membranes. Its oral LD_{50} is 2820 mg/kg for rats, which is of the same order of magnitude as that for trichloroacetic acid. Dichloroacetic acid is able to penetrate rabbit skin with a dermal LD_{50} of 797 mg/kg [140]. The lowest oral LD_{50} reported for dichloroacetate is 4480 mg/kg for fasted rats [141].

Sodium dichloroacetate was examined in a three-month oral toxicity study in rat and dogs. Both species manifested toxic effects, such as depressed appetites and increased body mass, degenerative changes of testicular germinal epithelium, hind limb muscular weakness or paralysis, and brain lesions. Cessation of administration brought about an amelioration or recovery from all effects except brain lesions. Dogs proved to be more sensitive than rats, showing toxic effects at $50 \text{ mg kg}^{-1} \text{ d}^{-1}$. The central nervous system (CNS) observations are extremely relevant in light of a report that described polyneuropathy of a 21-year-old man whose severe hypercholesterolemia had been treated orally with dichloroacetate (50 mg/kg) for 16 consecutive weeks. The polyneuropathy was characterized by weakness of facial, finger, and lower extremity muscles, by diminished deep tendon reflexes, and by slowing of nerve conduction velocity. The neuropathy improved when the therapy was stopped [147].

Dichloroacetate demonstrated low-grade mutagenicity in the Ames Salmonella/mammalian microsome mutagenicity test [148].

Trichloroacetic Acid and Trichloroacetate. Trichloroacetic acid is a strong protein precipitant and is corrosive to the skin and eye. The solid material is not readily absorbed through the skin [148]. The lowest reported oral LD_{50} in rats for trichloroacetic acid was 3320 mg/kg and 5060 mg/kg for trichloroacetate. The lowest lethal dose of trichloroacetate for female dogs was 1590 mg/kg with toxic effects, such as salivation, emesis, sedation, ataxia, and coma [149, 150]. A 4-h exposure to 4800 mg/kg trichloroacetate in ambient air did not result in any clinical symptoms or macroscopically detectable pathologic lesions in rats, guinea pigs, rabbits, and cats [150].

Medical reports of acute exposure effects of trichloroacetic acid showed mild to moderate skin and eye burns [151]. In humans, trichloroacetate was an irritant to skin and mucous membranes. Opaqueness of the cornea may occur. Oral ingestion led to intestinal colics, salivation, emesis, diarrhea, muscular weakness, anorexia, and apathy [150].

Little relevant chronic toxicity data exists for trichloroacetic acid. The toxicological profile of airborne trichloroacetic acid is assumed to be dominated by lesions of mucous membranes of the upper respiratory tract. A TLV-time weighted average (TWA) of 1 ppm , 7 mg/m^3 is suggested, based largely on analogy to 2,2-dichloropropionic acid (TLV-TWA 1 ppm , 6 mg/m^3) [151].

Trichloroacetic acid strongly binds to plasma proteins. A high concentration in blood is capable of displacing drugs from protein-binding sites. Because of this systemic effect of potential drug displacement from plasma proteins, a TLV of $1\text{--}2 \text{ ppm}$ may be accepted for trichloroacetic acid [149].

For trichloroacetate, a provisionally tolerated daily intake of 0.075 mg/kg body mass has been established. This limit value takes into account the results of a subchronic dog feeding study with concentrations in food of $\geq 2000 \text{ mg/kg}$, resulting in loss of body mass, malaise, necrosis of gingival and buccal mucosae, changes in white blood cell count, pathologic urine findings, lesions of the liver and myocardium, atrophy of

skeletal muscle, and impairment of spermiogenesis. The nontoxic effect level was 500 mg/kg in the diet [150].

On the basis of available in vitro data, trichloroacetate does not exert mutagenic effects [150].

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