

## CHLOROFORM

### 1. Introduction

Chloroform [67-66-3] (trichloromethane, methenyl chloride),  $\text{CHCl}_3$ , at normal temperature and pressure is a heavy, clear, volatile liquid with a pleasant, ethereal, nonirritant odor. Although chloroform is nonflammable, its hot vapor in admixture with vaporized alcohol burns with a green tinged flame. Chloroform is miscible with the principal organic solvents and is slightly soluble in water. It is less stable in storage than either methyl or methylene chloride. Chloroform decomposes at ordinary temperatures in sunlight in the absence of air and in the dark in the presence of air. Phosgene is one of the oxidative decomposition products.

Chloroform was discovered in 1831 by Liebig and Soubeirain simultaneously. Liebig obtained chloroform by the action of alkali on chloral, and Soubeirain by reaction of bleaching powder with alcohol or acetone. Guthrie, in the United States, is also alleged to have discovered chloroform in 1831. In 1839, Dumas produced chloroform by heating alkali with trichloroacetic acid. In the following year, Regnault obtained it by chlorinating methyl chloride. Chloroform was first used in medicine as a stimulant, taken internally, and as an inhalant in cases of asthma. In November, 1847, on the suggestion of Waldie, a Liverpool chemist, Simpson used chloroform as a total anesthetic in obstetrics.

Shortly after Simpson's successful use of chloroform in Edinburgh, Fraser began making pure anesthetic chloroform on a small scale in Nova Scotia.

In 1900, the Pennsylvania Salt Manufacturing Co. initiated large-scale production in the United States. The Midland Chemical Co., a subsidiary of The Dow Chemical Company, began to manufacture chloroform by reducing carbon tetrachloride in 1903. Chloroform was one of the first organic chemicals produced on a large scale in the United States.

Chloroform was used chiefly as an anesthetic and in pharmaceutical preparations immediately prior to World War II. However, these uses have been banned. Annual output in both the United States and the United Kingdom was between 900 and 1350 metric tons. During the war, chloroform production in the United States tripled, largely to meet the requirement for penicillin manufacture. Demand for chloroform continued to increase in the postwar period as its technical applications were extended. Consumption continues to increase at a comparatively rapid rate. Chloroform is now used primarily in the manufacture of HCFC-22, monochlorodifluoromethane, a refrigerant, and as a raw material for polytetrafluoroethylene plastics.

### 2. Physical and Chemical Properties

The physical properties of chloroform are listed in Table 1.

Chloroform dissolves alkaloids, cellulose acetate and benzoate, ethylcellulose, essential oils, fats, gutta-percha, halogens, methyl methacrylate, mineral oils, many resins, rubber, tars, vegetable oils, and a wide range of common organic compounds. A temperature increase occurs when chloroform is mixed

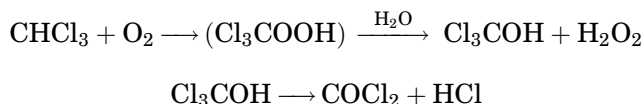
Table 1. Physical Properties of Chloroform

Property	Value
mol wt	119.38
refractive index at 20°C	1.4467
autoignition temperature, °C	above 1000
flash point, °C	none
mp, °C	−63.2
101 MPa <sup>a</sup>	−43.4
507 MPa <sup>a</sup>	20.4
1216 MPa <sup>a</sup>	112.6
bp at 101 kPa <sup>b</sup> , °C	61.3
sp gr	
0/4°C	1.52637
25/4°C	1.48069
60.9/4°C	1.4081
vapor density at 101 kPa <sup>b</sup> , 0°C, kg/m <sup>3</sup>	4.36
surface tension, mN/m (= dyn/cm)	
air, 20°C	27.14
air, 60°C	21.73
water, 20°C	45.0
heat capacity at 20°C, kJ/(kg · K) <sup>c</sup>	0.979
critical temperature, °C	263.4
critical pressure, MPa <sup>a</sup>	5.45
critical density, kg/m <sup>3</sup>	500
critical volume, m <sup>3</sup> /kg	0.002
thermal conductivity at 20°C, W/(m · K)	0.130
coefficient of cubical expansion	0.001399
dielectric constant, 20°C	4.9
dipole moment, C · m <sup>d</sup>	$3.84 \times 10^{-30}$
heat of combustion, MJ/(kg · mol) <sup>c</sup>	373
heat of formation at 25°C, MJ/(kg · mol) <sup>c</sup>	
gas	−89.66
liquid	−120.9
latent heat of evaporation at bp, kJ/kg <sup>c</sup>	247
solubility of chloroform in water, g/kg H <sub>2</sub> O	
0°C	10.62
20°C	8.22
30°C	7.76
solubility of water in chloroform, at 22°C, g/kg chloroform	0.806
viscosity, liq, mPa · s (= cP)	
−13°C	0.855
0°C	0.700
20°C	0.563
30°C	0.510

<sup>a</sup>To convert MPa to atm, multiply by 9.87.<sup>b</sup>To convert kPa to mm Hg, multiply by 7.5.<sup>c</sup>To convert J to cal, divide by 4.184.<sup>d</sup>To convert C · m to debye, divide by  $3.336 \times 10^{-30}$ .

with diethyl ether. Chloroform forms a series of binary azeotropes (1); the azeotrope with water boils at 56.1°C and contains 97.2% chloroform. The ternary azeotrope with ethanol and water boils at 55.5°C and contains 4 mol % alcohol and 3.5 mol% water. At 25°C, chloroform dissolves 3.59 times its volume of carbon dioxide.

Chloroform slowly decomposes on prolonged exposure to sunlight in the presence or absence of air and in the dark in the presence of air. The products of oxidative breakdown include phosgene, hydrogen chloride, chlorine, carbon dioxide, and water. At 290°C, chloroform vapor is not attacked by oxygen. In contact with iron and water hydrogen peroxide is also produced, probably by the following reaction sequence (2):



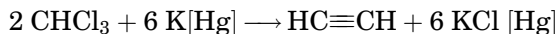
Oxidation with powerful oxidizing agents, eg, chromic acid, results in the formation of phosgene and the liberation of chlorine. Nitrogen dioxide at about 270°C oxidizes chloroform to a mixture of compounds including phosgene, hydrogen chloride, water, and carbon dioxide (3). Ozone forms a blue solution in chloroform and causes rapid decomposition.

Chloroform and water at 0°C form six-sided crystals of a hydrate,  $\text{CHCl}_3 \cdot 18\text{H}_2\text{O}$  [67922-19-41], which decompose at 1.6°C. Chloroform does not decompose appreciably when in prolonged contact with water at ordinary temperature and in the absence of air. However, on prolonged heating with water at 225°C, decomposition to formic acid, carbon monoxide, and hydrogen chloride occurs. A similar hydrolysis takes place when chloroform is decomposed at elevated temperature by potassium hydroxide.



Reaction of chloroform with hydroxide, particularly in the presence of methanol, can result in an explosion.

Chloroform resists thermal decomposition at temperatures up to about 290°C. Pyrolysis of chloroform vapor occurs at temperatures above 450°C, producing tetrachloroethylene, hydrogen chloride, and a number of chlorohydrocarbons in minor amounts (4,5). Pyrolysis in contact with hot pumice is catalyzed by vaporized iodine (1%), resulting in tetrachloroethylene, hexachloroethane, and carbon tetrachloride. Hexachlorobenzene, carbon monoxide, hydrogen chloride, and titanium tetrachloride are formed when chloroform vapor is decomposed by hot titanium oxide. In contact with potassium amalgam or red-hot copper, chloroform reacts to give acetylene.



Small quantities of ethyl alcohol stabilize chloroform during storage. Various other stabilizers have been proposed, eg,  $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CN}$  and methacrylonitrile (6).

Chloroform can be reduced to methane with zinc dust and aqueous alcohol. In the presence of a catalyst or ammonia, the reduction yields methylene chloride as well as methane.

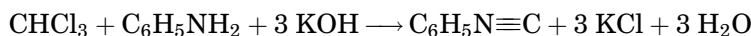
Chloroform reacts readily with halogens or halogenating agents. Chlorination of the irradiated vapor is believed to occur by a free-radical chain reaction (7).

At 225–275°C, bromination of the vapor yields bromochloromethanes:  $\text{CCl}_3\text{Br}$ ,  $\text{CCl}_2\text{Br}_2$ , and  $\text{CClBr}_3$ . Chloroform reacts with aluminum bromide to form bromoform,  $\text{CHBr}_3$ . Chloroform cannot be directly fluorinated with elementary fluorine; fluoroform,  $\text{CHF}_3$ , is produced from chloroform by reaction with hydrogen fluoride in the presence of a metallic fluoride catalyst (8). It is also a coproduct of monochlorodifluoromethane from the  $\text{HF}-\text{CHCl}_3$  reaction over antimony chlorofluoride. Iodine gives a characteristic purple solution in chloroform but does not react even at the boiling point. Iodoform,  $\text{CHI}_3$ , may be produced from chloroform by reaction with ethyl iodide in the presence of aluminum chloride; however, this is not the route normally used for its preparation.

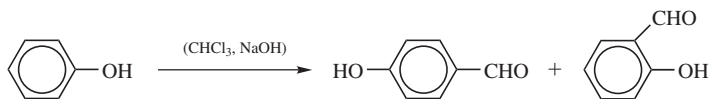
No decomposition occurs when boiling chloroform is in prolonged contact with anhydrous aluminum chloride; a double compound is formed from which unchanged chloroform is liberated by the action of water. With benzene in the presence of aluminum chloride, chloroform reacts to give triphenylmethane,  $(\text{C}_6\text{H}_5)_3\text{CH}$ , which is also formed from chloroform and phenylmagnesium bromide,  $\text{C}_6\text{H}_5\text{MgBr}$ .

In the presence of an alkali metal hydroxide at about 50°C, chloroform condenses with acetone to give 1,1,1-trichloro-2-methyl-2-propanol, [57-15-8] ie, chlorobutanol, chloretone, or acetone–chloroform (9,10). Chlorobutanol is a white crystalline substance with a camphorlike odor; its sedative, anesthetic, and antiseptic properties have given the compound some importance in the pharmaceutical industry.

Chloroform reacts with aniline and other aromatic and aliphatic primary amines in alcoholic alkaline solution to form isonitriles, ie, isocyanides, carbylamines, as shown:



Phenylisonitrile has a powerful characteristic odor; it is used as a qualitative test (the carbylamine test) for chloroform or primary aromatic amines. Chloroform reacts with phenols in alkaline solution to give hydroxyaromatic aldehydes in the Reimer-Tiemann reaction; eg, phenol gives chiefly *p*-hydroxybenzaldehyde and some salicylaldehyde (11) (see HYDROXYBENZALDEHYDES).



Chloroform combines with the inner anhydride of salicylic acid to form a well-defined crystalline double compound (12):



This complex readily liberates chloroform when heated and this reaction has been used to produce very pure chloroform.

Reactivities of several chlorinated solvents, including chloroform, with aluminum, iron, and zinc in both dry and wet systems have been determined, as have chemical reactivities in oxidation reactions and in reactions with amines (11). Unstabilized wet chloroform reacts completely with aluminum and attacks zinc at a rate of  $>250 \mu\text{m/yr}$  and iron at  $<250 \mu\text{m/yr}$ . The dry, uninhibited solvent attacks aluminum and zinc at a rate of  $250 \mu\text{m/yr}$  and iron at  $25 \mu\text{m/yr}$ .

### 3. Manufacture

Chloroform can be manufactured from a number of starting materials. Methane, methyl chloride, or methylene chloride can be further chlorinated to chloroform, or carbon tetrachloride can be reduced, ie, hydrodechlorinated, to chloroform. Methane can be oxychlorinated with HCl and oxygen to form a mixture of chlorinated methanes. Many compounds containing either the acetyl ( $\text{CH}_3\text{CO}$ ) or  $\text{CH}_3\text{CH}(\text{OH})$  group yield chloroform on reaction with chlorine and alkali or hypochlorite. Methyl chloride chlorination is now the most common commercial method of producing chloroform. Many years ago chloroform was almost exclusively produced from acetone or ethyl alcohol by reaction with chlorine and alkali.

**3.1. Methane or Chloromethane Chlorination.** This chlorination reaction is generally carried out in the gas phase at  $400\text{--}500^\circ\text{C}$  making all of the more heavily chlorinated products in substantial yields (see METHYLENE CHLORIDE). It is carried out by mixing the organic feed with gaseous chlorine and heating to initiate the reaction. Once started, this free-radical process rapidly goes to completion with the generation of substantial amounts of heat. This heat is transferred back to heat the feed stream. The reaction is controlled by limiting the amount of one of the feeds, generally the chlorine. The use of two reactors in parallel using different organic feed compositions is known (12,13).

The product selectivity of the chlorination of methane has been adequately described (14) over the whole range of products from methyl chloride to carbon tetrachloride. The presence of partially chlorinated chloromethanes in the reactor feed stream tends to change the product mix toward the more heavily chlorinated products. These partially chlorinated chloromethanes can be gases recycled from the product recovery equipment. Thus there is a fair degree of flexibility in tailoring product selectivity. The most common feed material for this process is methyl chloride. Use of methane as a feed material generally requires the production of the less desirable aqueous HCl and is not widely used industrially. In either case, to maximize chloroform production, product methyl chloride and methylene chloride are usually recycled back to the reactor. Numerous variations have been suggested as ways to increase the selectivity to a desired product. Tokuyama Soda has developed and practices a liquid-phase process based on methyl chloride chlorination (15–17). Light-initiated processes also claim enhanced selectivity (18). A novel process where chlorine atoms, the chain carriers in the free-radical reaction, are generated and transported to a reaction zone has been described (19,20). Fluidized beds have been suggested as a method of handling the large amount of heat generated and affecting selectivity with the proper choice of catalyst (21).

**3.2. Oxychlorination of Methane.** The oxychlorination of methane with HCl and oxygen has received some attention since the 1970s (22–24), though there are no examples of an industrial process. This can be a coproduct process making all the chloromethanes in significant yields or one that makes primarily methyl chloride. Interest in this route has increased in the past few years because of progress in the methane to light hydrocarbons process.

**3.3. Hydrogenation of Carbon Tetrachloride.** Carbon tetrachloride can be hydrogenated, ie, hydrodechlorinated, to chloroform over a catalyst (25,26) or thermally (27). Although there are no industrial examples of this process at this time, it will receive more attention as more carbon tetrachloride becomes available as the CFC-11 and -12 markets decline (see CARBON TETRACHLORIDE). Chloroform can be further hydrodechlorinated to methylene chloride (28,29).

A catalyst based on platinum dispersed throughout its support of gamma alumina for the production of chloroform via the hydrodechlorination of carbon tetrachloride has been described (30).

**3.4. Reduction of Alcohols or Ketones.** The reaction of alcohols and ketones with chlorine and base to give chloroform is well known (31). This was an industrial process for chloroform, but there are no plants currently using this technology. This reaction is possibly an important source of chloroform in the water treating process.

## 4. Economic Aspects

Table 2 lists the U.S. producers of chloroform and their capacities. Chloroform is coproduced with methylene chloride in direct reaction of methyl chloride with chlorine.

Demand for chloroform was  $274 \times 10^6$  kg ( $606 \times 10^6$  lb) in 1999. Expected demand for 2003 is  $298 \times 10^6$  kg ( $656 \times 10^6$  lb) (32). Growth is expected at a rate of 2% through 2003.

Price history for the years 1994 through 1999 was a high of \$0.20/kg (\$0.44/lb) technical consumers, tanks, dlv'd., list and the low was \$0.18/kg (\$0.395/lb) same basis.

HCFC-22 has grown at an annual rate of 3.2% in recent years as a replacement for chlorofluorocarbons in home and automobile air conditioners and commercial freezers. HCFC is also strong as a feedstock in the preparation of

Table 2. **United States Producers of Chloroform and Their Capacities<sup>a</sup>**

Producer	Capacity, $\times 10^6$ kg ( $\times 10^6$ lb)	
Dow, Freeport, Texas	91	(200)
Dow, Plaquemine, La	91	(200)
Vulcan, Geismar, La	73	(160)
Vulcan, Wichita, Kans.	73	(160)
<i>Total</i>	328	(720)

<sup>a</sup>Ref. 31.

polytetrafluoroethylene and fluorinated ethylene–propylene. However, use of HCFC as a refrigerant is subject to substitution by other products not subject to legislated restrictions. Beginning in 2010, production will go to feedstock use only and for refrigeration in equipment manufactured prior to 2010. Fluoropolymers will continue to rise because of demand for high performance wire and cable insulation.

## 5. Specifications and Standards

Technical-grade chloroform generally contains one or more stabilizers, which vary according to specification requirements. The most common is 50 ppm 2-methyl-2-butene [513-35-9]. Other stabilizers are industrial methylated spirit (0.2%), absolute alcohol (0.6–1%), thymol, *t*-butylphenol, or *n*-octylphenol (0.0005–0.01%). A representative technical quality chloroform contains the following amounts of the indicated substances (maximum):

water	50 ppm
acid (as HCl)	10 ppm
methylene chloride	200 ppm
bromochloromethane	300 ppm
carbon tetrachloride	250 ppm
1,2-dichloroethylene	100 ppm
vinylidene chloride	100 ppm
residue (on evaporation at 110°C)	10 ppm
dissolved chlorine	not detectable

## 6. Analytical Methods

The most widely used method of analysis for chloroform is gas chromatography. A capillary column medium that does a very good job in separating most chlorinated hydrocarbons is methyl silicone or methyl (5% phenyl) silicone. The detector of choice is a flame ionization detector. Typical molar response factors for the chlorinated methanes are methyl chloride, 2.05; methylene chloride, 2.2; chloroform, 2.8; and carbon tetrachloride, 3.1, where methane is defined as having a molar response factor of 2.00. Most two-carbon chlorinated hydrocarbons have a molar response factor of about 1.0 on the same basis.

In the known absence of bromoform, iodoform, chloral, and other halogenated methanes, the formation of phenylisocyanide with aniline provides a simple and fairly sensitive but nonspecific test for the presence of chloroform, the carbylamine test. Phenylisocyanide formation is the identification test given in the *British Pharmacopoeia*. A small quantity of resorcinol and caustic soda solution (10% concentration) added to chloroform results in the appearance of a yellowish red color, fluorescing yellow-green. When 0.5 mL of a 5% thymol solution is boiled with a drop of chloroform and a small quantity of potassium hydroxide solution, a yellow color with a reddish sheen develops; the addition of sulfuric

acid causes a change to brilliant violet, which, diluted with water, finally changes to blue (33).

Chloroform may be estimated quantitatively by determining the amount of copper oxide produced when it is warmed with Fehling's solution, which is potassium cupritartrate (34). An alternative procedure consists of heating the chloroform with concentrated alcoholic potassium hydroxide in a sealed tube at 100°C and determining the amount of potassium chloride produced (35).

## 7. Health and Safety Factors

**7.1. Handling.** All persons who have occasion to use or handle chloroform should be thoroughly instructed and adequately supervised in the proper methods of handling the substance to prevent or minimize exposure to the liquid or its vapors and in the proper methods of disposing of this chemical.

Chloroform should be stored in sealed containers in a cool place. Glass containers should be dark green or amber. Bulk storage containers may be constructed of mild or plain steel that is galvanized or suitably lined. Aluminum is not recommended for bulk storage. All bulk storage tanks should be equipped with a vent dryer packed with calcium chloride or other appropriate desiccant to exclude moisture. Alternatively, the tank may utilize a dry inert gas pad with an appropriate pressure vacuum relief valve, which is the recommended procedure, with appropriate disposal of the tank vents. Seamless stainless steel, Teflon, seamless bronze, or seamless steel hose is recommended with asbestos, Teflon, Viton, or Neoprene gaskets (36). Chloroform is transported in drums, truck transports, rail cars, barges, and oceangoing ships.

**7.2. Toxicology.** The principal hazard in exposure to chloroform is damage to the liver and kidneys resulting from inhalation or ingestion. Inhalation of high concentrations may result in disturbances of equilibrium or loss of consciousness. Chloroform is mildly irritating to skin and mucous membranes upon contact, and to the alimentary tract upon ingestion. It is believed that medically significant quantities are not absorbed through intact skin.

The toxic effects of chloroform resemble those of carbon tetrachloride. The probable effects of exposure to various atmospheric concentrations of chloroform are summarized in Table 3 (37).

In the past, chloroform was used extensively as a surgical anesthetic, but this use was abandoned because exposure to narcotic concentrations often resulted in sudden death from effects on the heart and circulation or from severe injury to the liver. In addition, chloroform for this and other consumer uses was banned by FDA in 1976 with the discovery that it is carcinogenic in mice (38). When splashed into the eye, chloroform causes local pain and irritation, but serious injury is not expected. Skin contact for single, brief exposures ordinarily causes little or no local irritation.

Repeated or prolonged contact with the skin, especially under clothing, may result in local irritation and inflammation, and at elevated temperatures such as in the presence of an open flame, chloroform decomposes to form by-products, including phosgene, chlorine, and hydrogen chloride, all of which are severe irritants to the respiratory tract.



Table 3. Effects of Exposure to Chloroform

Concentration		Response
ppm	mg/L	
205–310	1–1.5	smallest amount that can be detected by smell
390	1.9	endured for 30 min without complaint
1,025	5	definite after effects; fatigue and headache still experienced hours after exposure
1,025	5	dizziness, intracranial pressure, and nausea after 7 min exposure
1,475	7.2	dizziness and salivation after a few minutes exposure
4,100	20	vomiting, sensation of fainting
14,340–16,400	70–80	narcotic limiting concentration

Ingestion of chloroform is followed immediately by a severe burning in the mouth and throat, pain in the chest and abdomen, and vomiting. Loss of consciousness and liver injury may follow depending on the amount swallowed. The tendency of chloroform to produce liver injury is significantly augmented in alcoholics and persons with nutritional deficiencies.

The most serious hazard of repeated exposure to chloroform inhalation is injury to the liver and kidneys. Evidence indicates that in humans, repeated exposure to atmospheric concentrations well below the odor threshold may cause such injury. Industrial experience has shown that daily exposure to concentrations below 100 ppm may result in a variety of nervous system and alimentary tract symptoms, in the absence of demonstrable evidence of injury (39). Injury to the liver is similar to but somewhat less severe than that caused by carbon tetrachloride. Kidney injury is usually associated with but less severe than liver injury.

NIOSH recognizes chloroform as a carcinogen, and recommends a STEL of 2 ppm; ACGIH, TLV TWA is 10 ppm, with an A3 designation. OSHA has a ceiling limit of 50 ppm. WHO has a drinking water guideline of 30 µg/L. IARC classifies chloroform as a group 2B (possibly carcinogenic to humans, and EPA as a B2, probable human carcinogen (40).

Treatment of chloroform poisoning is symptomatic; no specific antidote is known. Adrenalin should not be given to a person suffering from chloroform poisoning.

**7.3. Regulations.** The NTP database gives the following information. EPA regulates chloroform under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Chloroform is a toxic pollutant of air and water. EPA has established water-quality criteria for chloroform, effluent guidelines, rules for regulating hazardous spills, general threshold amounts, and requirements for handling and disposal of chloroform wastes. A reportable quantity (RQ) of 10 lb has been

established for chloroform under CERCLA and CWA. Chloroform is exempted under FD&CA from tolerances for pesticide chemicals. Chloroform is recognized as an inert ingredient of toxicological concern under FD&CA. A rebuttable presumption against registration of chloroform-containing pesticides has been issued under FIFRA. Chloroform is regulated as a hazardous constituent of waste under RCRA. USEPA requires removal of chloroform from drinking water and establishes a maximum contaminant level (MCL) of 100 mg/L under SDWA. Under EPCRA, EPA identifies chloroform as an extremely hazardous substance and established a threshold planning quantity (TPQ) of 10,000 lb for chloroform. FDA regulates chloroform as an indirect food additive for adhesive components in food packaging materials and as a component of materials that come into contact with food. The use of chloroform in food, drugs (for both humans and animals), and cosmetics for use in cough preparations, liniments, cosmetics, and toothache drops is banned under the Federal Food, Drug, and Cosmetic Act.

## 8. Uses

About 95% of the chloroform produced goes into the production of HCFC-22 (chlorodifluoromethane [75-45-6]). Of this 95% about 70% is used as a refrigerant and about 30% is used as a starting material in the production of fluoropolymers, such as polytetrafluoroethylene (PTFE). Miscellaneous uses of the remaining 5% of the chloroform production include laboratory reagents and extractive solvents for pharmaceuticals (32).

The miscellaneous uses include extraction and purification of penicillin, alkaloids, vitamins, and flavors, and as an intermediate in the preparation of dyes and pesticides. A biologically active chloroform extract from mangrove plants has been described (41). Use as an antispasmodic, antiarrhythmic agent, or anticholinergic agent are possible. Chloroform has also been used as a fumigant and insecticide, in the formulation of cough syrups, toothpastes, liniments, and toothache preparations. These latter uses were banned by the FDA in 1976 (38).

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MICHAEL T. HOLBROOK  
Dow Chemical U.S.A.