CHLOROFORM	ICSC: 0027

Date of Peer Review:
April 2000

Trichloromethane
Methane trichloride
Formyl trichloride

CAS #	67-66-3	$CHCl_3$
RTECS #	FS9100000	Molecular mass: 119.4
UN #	1888	
EC #	602-006-00-4	

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Not combustible. See Notes. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**STRICT HYGIENE! AVOID EXPOSURE OF ADOLESCENTS AND CHILDREN!**	
Inhalation	Cough. Dizziness. Drowsiness. Headache. Nausea. Unconsciousness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Dry skin.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain.	Face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Vomiting. (Further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Give plenty of water to drink. Rest. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING

Evacuate danger area! Consult an expert! Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. Personal protection: complete protective clothing including self-contained breathing apparatus.	Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs. **EU Classification** Symbol: Xn R: 22-38-40-48/20/22 S: (2-)-36/37 **UN Classification** UN Hazard Class: 6.1 UN Pack Group: III
EMERGENCY RESPONSE	**SAFE STORAGE**
Transport Emergency Card: TEC (R)-61S1888 NFPA Code: H 2; F 0; R 0;	Separated from food and feedstuffs and incompatible materials, (see Chemical Dangers). Ventilation along the floor.

IPCS
International Programme on Chemical Safety

SEE IMPORTANT INFORMATION ON BACK

CHLOROFORM

ICSC: 0027

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE:
VOLATILE COLOURLESS LIQUID, WITH CHARACTERISTIC ODOUR.

PHYSICAL DANGERS:
The vapour is heavier than air.

CHEMICAL DANGERS:
On contact with hot surfaces or flames this substance decomposes forming toxic and corrosive fumes (hydrogen chloride ICSC0163, phosgene ICSC0007 and chlorine fumes ICSC0126). Reacts violently with strong bases, strong oxidants, some metals, such as aluminium, magnesium and zinc, causing fire and explosion hazard. Attacks plastic, rubber and coatings.

OCCUPATIONAL EXPOSURE LIMITS:
TLV: 10 ppm as TWA; A3 (confirmed animal carcinogen with unknown relevance to humans); (ACGIH 2004).
MAK: 0.5 ppm, 2.5 mg/m^3; Peak limitation category: II(2); skin absorption (H); Carcinogen category: 4; Pregnancy risk group: C; (DFG 2004).

ROUTES OF EXPOSURE:
The substance can be absorbed into the body by inhalation, through the skin and by ingestion.

INHALATION RISK:
A harmful contamination of the air can be reached very quickly on evaporation of this substance at 20℃.

EFFECTS OF SHORT-TERM EXPOSURE:
The substance is irritating to the eyes. The substance may cause effects on the central nervous system, liver and kidneys. The effects may be delayed. Medical observation is indicated.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:
The liquid defats the skin. The substance may have effects on the liver and kidneys. This substance is possibly carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: 62℃ Melting point: -64℃ Relative density (water = 1): 1.48 Solubility in water, g/100 ml at 20℃: 0.8 Vapour pressure, kPa at 20℃: 21.2 Relative vapour density (air = 1): 4.12	Relative density of the vapour/air-mixture at 20℃ (air = 1): 1.7 Octanol/water partition coefficient as log Pow: 1.97

ENVIRONMENTAL DATA

The substance is toxic to aquatic organisms.

NOTES

Turns combustible on addition of small amounts of a flammable substance or an increase in the oxygen content of the air. Use of alcoholic beverages enhances the harmful effect. Depending on the degree of exposure, periodic medical examination is indicated. The odour warning when the exposure limit value is exceeded is insufficient. Do NOT use in the vicinity of a fire or a hot surface, or during welding.
Card has been partly updated in April 2005. See section Occupational Exposure Limits.

ADDITIONAL INFORMATION

CHLOROFORM

International Programme on Chemical Safety
Poisons Information Monograph 121
Chemical

1. NAME

1.1 Substance

Trichloromethane

1.2 Group

Organochlorine solvent

1.3 Synonyms

chloroform (Dutch, German, Polish),
chloroform (IUPAC),
chloroforme (French),
chloroformium anaestheticum,
chloroformum,
chloroformum pro narcosi,
cloroformio,
formyl trichloride,
methane trichloride,
methenyl chloride,
methenyl trichloride,
methyl trichloride,
trichloormethaan (Dutch),
trichlormethan (Czech),
trichloroform,
triclorometano (Italian),

1.4 Identification numbers

1.4.1 CAS number

67-66-3

1.4.2 Other numbers

1888 (UN)
FS9100000 (NIOSH)
UN Hazard class: 6.1 (poisonous substances)

1.5 Main brand names, main trade names

Freon 20, NCI-C02686, R20, R20 (refrigerant)

1.6 Main manufacturers, main importers

Produced by many manufacturers and widely imported.

2. SUMMARY

2.1 Main risks and target organs

Acutely, CNS depression and respiratory arrest; late onset liver and kidney damage.

2.2 Summary of clinical effects

Acute poisoning with chloroform is uncommon. The main route of exposure is inhalation but in some cases poisoning is due to ingestion; skin absorption is limited. Central nervous system depression is the most prominent sign after acute exposure. Death may occur within few minutes of heavy exposure from respiratory arrest or from ventricular fibrillation (cardiac arrest). The prognosis is favourable if consciousness is recovered but liver and kidney damage may then develop. Less severe exposure causes dizziness, dilated pupils, nausea, vomiting.

2.3 Diagnosis

Headache, impaired consciousness, convulsions, respiratory paralysis, dizziness, abdominal pain, nausea, vomiting and diarrhoea are the feature of chloroform poisoning following ingestion There may be dizziness and short of breath following inhalation.

Later, symptoms of liver and kidney may develop. The main features of acute poisoning do not depend on the route of entry but rather on the amount of chloroform absorbed by the body.

Analysis of biological fluids plays no role in the diagnosis of acute poisoning.

2.4 First-aid measures and management principles.

Management consists of early decontamination, supportive treatment with respiratory and cardiac monitoring, avoidance of catecholamine drugs and treatment of hepatic and or kidney failure if they occur.

3. PHYSICO-CHEMICAL PROPERTIES

3.1 Origin of the substance

Although negligible amounts of chloroform may be produced naturally in the atmosphere (Ross et al., 1978) and in soil and water (Clayton & Clayton, 1981), manufacturing is the main source.

Chloroform is usually manufactured by two processes - hydrochlorination and then further chlorination of methanol or chlorination of methane (GCA Corporation, 1984). Both processes yield a mixture of chloromethanes. Chloroform is then separated by sequential distillation.

3.2 Chemical structure

$CHCl_3$

Molecular weight 113.4

3.3 Physical properties

3.3.1 Colour

3.3.2 State/Form

3.3.3 Description

Boiling point: 61.15°C - 61.70°C.
Melting point: -63.2 - -63.5°C at atmospheric pressure.
Flash point: none.
Relative vapour density (air = 1): 4.1 - 4.36 kg/m at 101 kPa, 0°C.

Vapour pressure:	21.15 kPa at 20°C.
Solubility in water:	10.62g/kg at O°C
	8.95g/kg at 10°C
	8.22g/kg at 20°C
Specific gravity:	1.483 at 20°C

Chloroform is miscible with acetone, benzene, carbon disulphide, carbon tetrachloride, ethanol, ether, petroleum ether, fixed and volatile oils and most organic solvents.

Concentration Conversion Factors
1 mg/l = 206 ppm 1 ppm = 4.89 mg/m3 at 25°C and atmospheric pressure (Royal Society of Chemistry, 1986)

3.4 Hazardous characteristics

At normal temperature and pressures, chloroform is a heavy, very volatile, clear, colourless, highly refractive, non inflammable liquid. It has a characteristic sweet, ethereal odour and a sweetish burning taste. The odour is not irritant. Pure chloroform is light, sensitive and reagent grade chloroform usually contains 0.75% ethanol as stabilizer (Merck).

Chloroform reacts vigorously with acetone in the presence of KOH or CaOH. It may also react explosively with fluorine, dinitrogen tetraoxide, aluminium, lithium, sodium, sodium/methanol, NaOH/methanol, sodium methoxide and triisopropylphosphine (Sax, 1984; Bretherick, 1979). Mixtures of chloroform and nitromethane are said to be detonable (Bretherick, 1979).

Chloroform is oxidized by strong oxidizing agents such as chromic acid with formation of phosgene and chlorine gas.

Chloroform may generate the highly toxic gas phosgene if it comes into contact with flames or hot metal surfaces (NIOSH, 1979a). When heated to decomposition it emits toxic fumes of chlorine (Sax, 1984).

Chloroform explodes when in contact with aluminium powder or magnesium powder.

4. USES

4.1 Uses

4.1.1 Uses

4.1.2 Description

The main use of chloroform is the production of other materials,principally fluorocarbons (for example, chlorodifluoromethane) used in the synthesis of tetrafluoroethylene and polytetrafluoroethylene, and as a refrigerant and propellant. Chloroform is also widely employed as an organic solvent in industryand in analytical laboratories. It has also been used as an ingredient of pharmaceuticals, drugs, cosmetics, grain fumigants, dyes and pesticides. The United States Food and Drug Administration listed some 1900 human drug products containing chloroform in 1976 (IARC, 1979) but its pharmaceutical use has been restricted in many countries. Chloroform may be a drug of abuse.

Worldwide production of chloroform in 1973 was about 2.5 million tonnes (Ross et al., 1978).

4.2 High risk circumstance of poisoning

Exposure may be occupational or by voluntary ingestion or inhalation for its psychotropic effects (Hutchens 1985; Storms,1973; Iffland & Ramme, 1983; Beer et al., 1984).

4.3 Occupationally exposed populations

High risk circumstances of acute and chronic poisoning occur mostly in chemical plants where chloroform is manufactured and used and in chemical laboratories which use chloroform as a solvent. Transport and storage of improperly closed containers also creates a high risk. Chronic exposure may occur in farmers using pesticides containing chloroform (for instance, grain fumigants); in people dealing with drugs and cosmetics containing chloroform; and in users of such products.

5. ROUTES OF EXPOSURE

5.1 Oral

Acute poisoning may be due to accidental or deliberate ingestion. Chloroform is readily absorbed through mucous membranes (Davidson et al., 1978). Although water, food and oral drugs contain minute amounts of chloroform, significant chronic poisoning is unlikely by this route.

5.2 Inhalation

Inhalation is the most frequent and the most important route of entry of chloroform. Poisoning by this route is also best understood from experience of its use as a general anaesthetic until it was replaced by less toxic compounds.

Up to 64-67% of chloroform from inspired air is retained in the body. Pulmonary intake is directly related to the chloroform concentration in the air, the ventilation volume and to the duration of exposure (Davidson et al.,1978).

5.3 Dermal

Dermal exposure may cause irritation (especially of the most sensitive areas such as the anogenital region and, although absorption via this route is usually not significant, systemic effects changes may occur which resembling those produced by inhalation (Royal Society of Chemistry, 1986).

5.4 Eye

Liquid chloroform irritates the eye but systemic absorption is not significant.

5.5 Parenteral

Parenteral administration may be an act of deliberate self poisoning, criminal poisoning or medical error.

5.6 Others

No data available.

6. KINETICS

6.1 Absorption by route of exposure

The gastrointestinal absorption of chloroform has not been satisfactorily studied but is said to occur readily; the peak blood concentration occurs one hour after ingestion (Davidson et al., 1978).

Inhalation is the principal route of entry of chloroform into the body. The total quantity absorbed through the lungs is directly proportional to:

the concentration in the inspired air;
the exposure time;
the blood/air Ostwald solubility coefficient;
the solubility in the various body tissuesphysical activity.

The basic kinetic parameters of chloroform absorption by inhalation and its equilibration in the body apply equally to both low and high concentrations. At concentrations inducing anaesthesia (8000 - 10,000 ppm), a high blood level (about 100 mg/l) is obtained within a couple of minutes.

Skin exposure: rarely causes absorption of significant amounts of chloroform.

Ocular exposure: small amounts may be absorbed.

6.2 Distribution by route of exposure

The distribution of chloroform in the body does not differ qualitatively between the various routes of exposure. Chloroform is rapidly absorbed and distributed to all body tissues (IARC, 1979). Chloroform is lipophilic and therefore it concentrates mainly in lipid-containing organs such as adipose tissue, the central nervous system, kidney and liver. Chloroform remains in these tissues at least for several hours after exposure and accumulation of chloroform in the body will occur during repeated exposures.

Chloroform passes the placental barrier and it has been found in fresh cow's milk; it probably occurs in human colostrum and mature milk (Davidson et al., 1978).

6.3 Biological half-life by route of exposure

No data available.

6.4 Metabolism

Chloroform is extensively metabolized by the liver. Phosgene, carbene and chlorine are some of the metabolites which may account for its cytotoxic activity.

6.5 Elimination by route of exposure

The elimination of chloroform is not qualitatively affected by the route of exposure. About 60 - 70% is eliminated unchanged in expired air; 30 - 40% is metabolized and excreted in urine and faeces. Its metabolism is dose-dependent and may be proportionally higher at lower exposures (Davidson et al., 1979).

7. TOXICOLOGY

7.1 Mode of Action

Chloroform causes progressive depression of the central nervous system, ultimately producing deep coma and respiratory centre depression. It is also hepatotoxic and nephrotoxic, although liver and kidney damage can be influenced by various treatments which affect hepatic drug-metabolizing enzymes (IARC, 1979): induction of hepatic enzymes with barbiturates, DDT or ethanol potentiates hepatic cell necrosis and kidney damage (NIOSH, 1979b). The reactive intermediates of chloroform metabolism (phosgene, carbene and

Cl) which bind covalently and irreversibly to cellular macromolecules are believed to account for cellular damage within the liver and kidney (Davidson et al., 1978).

7.2 Toxicity

7.2.1 Human data

7.2.1.1 Adults

Chloroform has been widely used as an anaesthetic but it has now been abandoned due to its toxicity. Prolonged administration as an anaesthetic may lead to profound

toxaemia and damage to the liver, heart and kidneys. Inhalation of concentrated chloroform vapour causes irritation of exposed mucous surfaces. Narcosis is ordinarily preceded by a stage of excitation which is followed by loss of reflexes,sensation and consciousness.

7.2.1.2 Children

No specific data available.

7.2.2 Relevant animal data

Concentrations of 68,000 - 28,000 ppm kill most animals in a few minutes; 14,000ppm is dangerous to life after an exposure of 30 to 60 minutes; 5,000 to 6,000 ppm can be tolerated by animals for one hour without serious disturbances. The maximum concentration tolerated for several hours or for prolonged exposure with slight symptoms is 2,000 to 2,500 ppm. The harmful effects are narcosis, and damage to the liver and heart. Experimentally prolonged but light anaesthesia in dogs produces a typical hepatitis.

7.2.3 Relevant in vitro data

No recent references available providing reliable relevant information.

7.2.4 Workplace standards

NIOSH recommends a time-averaged limit of 10 ppm (NIOSH 1979b).

7.2.5 Acceptable daily intake (ADI) and other guideline levels

Data not available.

7.3 Carcinogenicity

There is sufficient evidence that chloroform is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable for practical purposes to regard chloroform as potentially carcinogenic in man (IARC, 1979). Animal data should be extrapolated to man only with caution. Nonetheless, when theoretical risk assessment models are applied to the available data, the estimated virtual human dose for a cancer risk of 1 per million is 0.26 mg/day or less. In animals, very low levels of chloroform (0.75 and 75 ppm) in the drinking water (equivalent to about 0.15 and 15 mg/kg/day in mice) appears to be sufficient to promote the growth and spread of tumours (Davidson et al., 1978).

7.4 Teratogenicity

Chloroform is teratogenic in the rat, mouse and rabbit (IARC, 1979) but human data are not available.

7.5 Mutagenicity

Chloroform is not mutagenic in animals; no human data are available (IARC, 1979).

7.6 Interactions

Chloroform is more hepatotoxic and nephrotoxic when administered after alcohols, barbiturates or DDT (NIOSH, 1979b).

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan

8.1.1 Sampling and specimen collection

8.1.1.1 Toxicological analyses

8.1.1.2 Biomedical analyses

8.1.1.3 Arterial blood gas analysis

8.1.1.4 Haematological analyses

8.1.1.5 Other (unspecified) analyses

8.1.2 Storage of laboratory samples and specimens

8.1.2.1 Toxicological analyses

8.1.2.2 Biomedical analyses

8.1.2.3 Arterial blood gas analysis

8.1.2.4 Haematological analyses

8.1.2.5 Other (unspecified) analyses

8.1.3 Transport of laboratory samples and specimens

8.1.3.1 Toxicological analyses

8.1.3.2 Biomedical analyses

8.1.3.3 Arterial blood gas analysis

8.1.3.4 Haematological analyses

8.1.3.5 Other (unspecified) analyses

8.2 Toxicological Analyses and their Interpretation

8.2.1 Tests on toxic ingredient(s) of material

8.2.1.1 Simple Qualitative Test(s)

8.2.1.2 Advanced Qualitative Confirmation Test(s)

8.2.1.3 Simple Quantitative Method(s)

8.2.1.4 Advanced Quantitative Method(s)

8.2.2 Tests for biological specimens

8.2.2.1 Simple Qualitative Test(s)

8.2.2.2 Advanced Qualitative Confirmation Test(s)

8.2.2.3 Simple Quantitative Method(s)

8.2.2.4 Advanced Quantitative Method(s)

8.2.2.5 Other Dedicated Method(s)

8.2.3 Interpretation of toxicological analyses

8.3 Biomedical investigations and their interpretation

8.3.1 Biochemical analysis

8.3.1.1 Blood, plasma or serum

8.3.1.2 Urine

8.3.1.3 Other fluids

8.3.2 Arterial blood gas analyses

8.3.3 Haematological analyses

8.3.4 Interpretation of biomedical investigations

8.4 Other biomedical (diagnostic) investigations and their interpretation

8.5 Overall Interpretation of all toxicological analyses and toxicological investigations

Collect samples of blood and urine for biomedical analyses mentioned below.

Estimation of chloroform or its metabolites in the body fluids plays no practical role in the management of acute or chronic poisoning.

Arterial O2, CO2 and pH should be monitored in cases of severe poisoning with respiratory failure.

Monitor serum bilirubin, transaminases, plasma prothrombin alkaline phosphatase and gamma-glutamyl transpeptidase to detect the degree of liver damage. In case of liver damage increased urinary concentrations of bilirubin may occur.

Daily urine collection, plasma creatinine and urea measurement are needed to detect renal failure.

Chloroform is toxic to the bone marrow and may also cause a deficiency of plasma prothrombin and fibrinogen. A full blood count should be performed; monitor plamsa prothrombin and fibrinogen (Winslow & Gerstner, 1978).

In severe cases, serum electrolytes, urea and creatinine should be monitored. Glucose may be elevated and ketoacidosis found due to the incomplete oxidation of fats (Winslow & Gerstner, 1978).

Estimation of chloroform or its metabolites in the body fluids plays no practical role in the management of acute or chronic poisoning.

Chloroform may be measured in the air of the workshop atmospheres using portable or static sampling devices (NIOSH, 1979a), in water and food (Kaiser & Oliver, 1976; Piet et al., 1978; Simmonds & Kerns, 1979; Gruber, 1984; Ploder, 1974; Pereira & Hughes, 1980) and in the biological fluids (blood, urine) or tissues of the poisoned person (Peoples et al., 1979).

The following spectroscopic data are available (Grasselli & Ritchley, 1975): infra-red, Raman, ultraviolet, nuclear magnetic resonance and mass spectrometry. The concentration of chloroform in air is measured, as recommended by NIOSH (1977), by an activated charcoal trapping method for collection and concentration, followed by solvent extraction of the charcoal and a gas chromatographic (GC) analysis of the extract.

The collection tube is 7 cm long with a 4 mm internal diameter. It contains a total of 150 g of activated charcoal (20-40 mesh), divided into a front section of 100mg and a rear section of 50mg separated by a plug of urethane foam. Air is sampled at a flow rate of 200 ml per minute by means of a small pump. The entire apparatus is portable and it may be carried in a pocket with the sampling tube in the breathing zone (normally a coat lapel). The apparatus can also be static.

Carbon disulphide is used to extract the chloroform, which is separated on a 6.10 m by 3.18 mm stainless steel packed with 10% FFAP on Chromosorb using flame ionization detection.

Water samples are purged with helium and the volatile substances including chloroform are trapped on Tenax-GC prior to GC analysis. A Tracor conductivity detector, operated in the catalytic pyrolysis mode, was used successfully in place of the usual electron capture detection (Pape, 1977).

Blood, serum and various adipose tissues were extracted with hexane the extract was heated at 115 C and the volatiles collected in a Tenac-silica gel trap (Peoples et al., 1979). Chloroform, together with carbon tetrachloride, 1,2-dichloroethane and trichloroethylene were thermally adsorbed and determined by GC on a 1.83 m by 6.35 mm column packed with Porasil C supporting octane. Temperature programming and a halide-specific detector were used.

8.6 References

9. CLINICAL EFFECTS

9.1 Acute poisoning

9.1.1 Ingestion

Clinical effects of acute poisoning are due to effects on both the central (headache, various degrees of impaired consciousness, convulsions, respiratory centre paralysis) and the autonomic nervous systems (dizziness, nausea, vomiting). These symptoms occur immediately after toxic exposure. Later, symptoms of liver and kidney may develop. The main features of acute poisoning do not depend on the route of entry but rather on the amount of chloroform absorbed by the body.

Direct irritation of the gastrointestinal tract causes abdominal pain, nausea, vomiting, diarrhoea; later involvement of the autonomic nervous system also causes nausea and vomiting.

9.1.2 Inhalation

Inhalation is the most frequent and most important route of poisoning with chloroform. Mild poisoning causes slight shortness of breath and dizziness. More severe poisoning causes nausea, vomiting, drowsiness and various levels of impaired consciousness, convulsions and respiratory centre paralysis.

Later, symptoms of liver and kidney may develop. The main features of acute poisoning do not depend on the route of entry but rather on the amount of chloroform absorbed by the body.

9.1.3 Skin exposure

Irritation and redness may occur at the site of contact, especially of the more sensitive skin parts (eyelids, neck, axillae, anogenital region) and burns may occur. Chloroform may be absorbed through the skin and cause systemic symptoms, although this route of absorption is not normally significant.

9.1.4 Eye contact

Eye contact with liquid chloroform results in painful irritation of the superficial eye structures, burns and may cause corneal necrosis and ulcers.

9.1.5 Parenteral exposure

Parenteral exposure is unlikely except as a result of a voluntary poisoning or medical error. The systemic effects appear very rapidly (see 9.1).

9.1.6 Other

No data available

9.2 Chronic poisoning

9.2.1 Ingestion

A man who ingested cough mixture containing 1.6 to 2.6 g of chloroform daily for 10 years developed hepatitis and nephrosis. Severe cellular changes were found on liver biopsy in another man who had ingested 21 ml of chloroform daily for an undetermined period. No evidence of harm could be found in users of a dentifrice containing 3.4% chloroform and a mouthwash containing 0.43% (Pohl, 1979).

Surprisingly few clinical data are available concerning chronic human exposure to chloroform despite its long history of use and there are almost no quantitative toxicological studies (Clayton and Clayton, 1981; IARC, 1979).

9.2.2 Inhalation

Habitual inhalation of 1 oz of chloroform daily for 7 years followed by 2 oz daily for a further 5 years was associated with delusions, restlessness, depression, convulsions, ataxia, dysarthria, tremor of the tongue and fingers, and insomnia (NIOSH, 1979b).

9.2.3 Skin exposure

No data available.

9.2.4 Eye contact

No data available.

9.2.5 Parenteral exposure

No data available.

9.2.6 Other

No data available.

9.3 Course, prognosis, cause of death

Acute poisoning with chloroform may follow a benign course and leave no permanent damage. However, after rapid absorption of high doses, death occurs quickly due to respiratory paralysis or cardiac arrest, especially when proper cardio-respiratory resuscitation is not available. If the patient survives this early dramatic phase, or when the exposure is less severe, moderate CNS depression is the most prominent effect of acute poisoning. The patient may be dizzy, stuporous or deeply unconscious and, if there is no further absorption, recovery occurs gradually 20-60 minutes after exposure, often with profuse vomiting.

Lower doses result in dizziness, salivation, a feeling of pressure within the head, nausea and vomiting.

After larger or repeated exposures, liver and, less frequently,overt kidney damage may develop after several days. This may be followed by complete recovery within several weeks but may also have a fatal outcome, sometimes even within less than a week (Winslow & Gerstner, 1978).

9.4 Systematic description of clinical effects

9.4.1 Cardiovascular

Early death after heavy exposure to chloroform may be due to ventricular fibrillation by a direct effect of chloroform on the myocardium, through vagal stimulation or by sensitizing the heart to endogenous or exogenous catecholamines (ILO, 1983). Chloroform also causes hypotension by decreasing the contractile power of myocardium and peripheral vasodilatation arising from vagal stimulation.

9.4.2 Respiratory

Respiratory failure is due to paralysis of the medullary respiratory centre, not a direct action of chloroform on the respiratory system or to the aspiration of vomitus.

9.4.3 Neurological

9.4.3.1 Central Nervous System (CNS)

Depression of the CNS and even coma are the most prominent effects of acute exposure.

Convulsions may occur. Paralysis of the respiratory centre may cause sudden death. Chronic exposure may cause restlessness, depression, convulsions, ataxia, dysarthria, tremor of the tongue and fingers and insomnia (NIOSH, 1979b).

9.4.3.2 Peripheral nervous system

No data available

9.4.3.3 Autonomic nervous system

Vagal stimulation is associated with dilatation of pupils, nausea, vomiting, salivation and profuse sweating (Clayton & Clayton, 1981). Vagal stimulation of the heart causes various cardiac and peripheral circulatory disturbances(see 9.1).

9.4.3.4 Skeletal and smooth muscle

Relaxation of vascular smooth muscle leads to hypotension (ILO, 1983).

9.4.4 Gastrointestinal

Ingested chloroform irritates the gastrointestinal mucosa and may even cause burns. It induces vomiting mostly through vagal stimulation but also by a direct local action. Diarrhoea may also occur (Winslow & Gerstner, 1978).

9.4.5 Hepatic

The hepatotoxicity of chloroform is probably due to the metabolites phosgene, carbene and chlorine produced by the liver. Necrosis of liver cells may occur (Winslow & Gerstner, 1978), causing increased concentrations of serum bilirubin and transaminases. Deficiency of prothrombin and fibrinogen may also occur (Winslow & Gerstner, 1978). Chronic exposure may cause liver damage although convincing evidence to support this is lacking (Pohl, 1979).

9.4.6 Urinary

9.4.6.1 Renal

Kidney damage is less common than injury to the liver but it may occur after acute exposure (Clayton & Clayton, 1981). Acute exposure may be associated with damage to the renal tubules, mainly involving the epithelium of Henle's loop (Winslow & Gerstner, 1978). The renal effect may be due to prolonged anoxia rather than to a direct toxic effect on the kidney since proper oxygenation seems to prevent renal damage (Waters, 1951).

9.4.6.2 Others

No data available.

9.4.7 Endocrine and reproductive systems

No data available.

9.4.8 Dermatological

Local irritation and burns have been observed, especially at the more sensitive skin areas.

9.4.9 Eye, ears, nose, throat: local effects

Conjunctivitis and corneal injury occur after eye contact. Oral mucosa may also be irritated.

9.4.10 Haematological

Chloroform may damage the erythrocyte membrane (NIOSH, 1979b); blood clotting may be impaired by deficiency of prothrombin and fibrinogen (Winslow & Gerstner, 1978).

9.4.11 Immunological

No data available.

9.4.12 Metabolic

9.4.12.1 Acid-base disturbances

Ketoacidosis may occur (Winslow & Gerstner, 1978).

9.4.12.2 Fluid and electrolyte disturbances

Secondary to losses occur due to vomiting and diarrhoea.

9.4.12.3 Others

Hyperglycaemia may occur in acute chloroform poisoning (Winslow & Gerstner, 1978).

9.4.13 Allergic reactions

No data available.

9.4.14 Other clinical effects

No data available.

9.4.15 Special risks

Pregnancy: No data available.

Breast feeding: Chloroform probably occurs in human colostrum and milk.

Enzyme deficiencies: No data available.

9.5 Others

No data available.

9.6 Summary

10. MANAGEMENT

10.1 General principles

Paralysis of the respiratory centre or cardiac arrest (due to ventricular fibrillation) may cause instant death if the proper resuscitation measures are not started immediately. The unconscious patient needs supportive treatment (under respiratory and cardiac monitoring) and possibly fluid replacement. Within a few days, hepatic and renal failure may develop. Forced diuresis, peritoneal or extracorporeal haemodialysis, haemoperfusion and plasmapheresis are useless in the management of acute chloroform poisoning but renal dialysis is essential if kidney failuredevelops.

10.2 Life supportive procedures and symptomatic treatment

Monitor respiratory and cardiac function. Respiratory assistance is often necessary and cardiac defibrillation may be needed.

Haemodynamic status should be monitored and balanced using intravenous administration of fluids and electrolytes.

10.3 Decontamination

Emptying the stomach after ingestion is of questionable value because the absorption of chloroform is very rapid. Milk, fat or fatty emulsions should not be given orally or by gastric tube because they may enhance absorption. Clothing soaked with chloroform should be removed. After eye contact, wash with copious amounts of water; wash contaminated skin with soap and water.

In case of spillage, instruct others to keep at a safe distance. Wear breathing apparatus and gloves. Apply a dispersing agent if available and work to an emulsion with a brush and wash into a waste system, diluting the chloroform greatly with copious running water. If a dispersant is not available, absorb the spillage with sand and shovel it into a bucket; transport this to a safe, open area so that it can evaporate into the air. The site of the spillage should be washed thoroughly with water and soap or detergent (Bretherick, 1981).

10.4 Enhanced elimination

No data available

10.5 Antidote treatment

10.5.1 Adults

Not known

10.5.2 Children

Not known

10.6 Management discussion

No data available

11. ILLUSTRATIVE CASES

11.1 Case reports from literature

A 19-year old man who was at a "chloroform party" consumed three bottles of beer and then mistakenly drank an unknown quantity of chloroform. He collapsed and was taken to a local emergency room, where he was found to be stuporous. His blood pressure was 110/60 mmHg. He was immediately transferred to the medical intensive care unit at the University of Wisconsin Hospital. By that time he was comatose, cyanosis was present, and his breathing was laboured. His blood pressure was 100/40 mmHg; pulse rate 108

beats per minute; and respiration 26/min. The only other relevant physical finding was hypoactive deep tendon reflexes.

Because of poor ventilatory effort, the patient was intubated and breathing was controlled on a volume ventilator. Hypoxia could be corrected only with continuous positive pressure ventilation. The initial haematocrit value, white blood cell count, urinalysis, all levels of blood urea nitrogen, electrolytes, fibrinogen, and blood glucose were normal. Euglobulin lysis took more than 24 hours. Liver function abnormalities during hospitalization and on follow-up examination are shown in the table.

Days Following Ingestion

	1	2	3	4	6	90
SGOT (IU)	30	681	8080	5300	297	34
SGPT (IU)	15	-	9220	10250	3330	
LDH (IU)	204	636	9280	5680	630	176
Total bilirubin (mg/dl)	0.2	2.3	2.4	2.7	1.3	1.0
Alkaline phosphatase (IU)	6.1	5.2	-	6.4	-	5.0
Prothrombin time (sec):						
Patient	14.3	19.3	-	18.4	14.3	12.3
Control	12.6	11.9	-	12.7	11.8	12.2

Ten hours after ingestion, the chloroform level in blood was 200 mg/l. Three days after admission, the patient began to respond and was extubated. Cerebellar damage was noted, characterized by instability of gait and a slight tremor on finger-to-nose testing. These findings returned to normal in two weeks. Liver function tests eight weeks after discharge were normal (Storms 1973).

12. ADDITIONAL INFORMATION

12.1 Specific preventive measures

The work place atmosphere should not contain more than 10 ppm of chloroform.

Shipping and storage containers should carry a label warning that chloroform is highly dangerous because of its toxic and carcinogenic properties (ILO, 1983). Containers of chloroform should be kept closed when not in use. Activities in which chloroform is used should be isolated and work should be performed with adequate ventilation. Workers should be trained to handle the material safely. Protective clothing, gloves, eye protection, shields and respirators should be provided. Recommendations for work practices, labelling, personal protective equipment, protective clothing and sanitation are included in the references (NIOSH, 1979a, 1979b)

12.2 Other

No data available.

13. REFERENCES

Beer J, Heer G, Schlup P (1984) Schweiz. med. Wschr., 114: 1538

Bretherick L (1979) Handbook of Reactive Chemical Hazards. 2nd ed., Butterworths

Bretherick L. ed. (1981) Hazards in the Chemical Laboratory, 3rd ed. The Royal Society of Chemistry

Clayton GD and Clayton FE, eds. (1981) Patty's Industrial Hygiene and Toxicology. Vol.2B. Toxicology. 3rd rev. ed.

John Wiley & Sons, Inc. Davidson IWF et al., (1978) Drug and Chemical Toxicology, 5: 259

GCA Corporation. Locating Estimating Air Emissions from Sources of Chloroform. Report No. EPA-450/4-84-007c. US Environment Protection Agency, March 1984

Grasselli JG, Ritchley WM, eds. (1975) Atlas of Spectral Data and Physical Constants for Organic Compounds. 2nd ed. CRC Press, Inc.

Gruber H (1984) GIT Fachzeitschrift fuer das Laboratorium, 28: 161

Hutchens KA, Kung M (1985) Am. J. Med., 78: 715

IARC (1979) IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Some Halogenated Hydrocarbons, IARC.

Iffland R, Ramme H (1983) Arch. Toxicol., 53: 289

ILO (1983) Encyclopedia of Chemicals, Drugs and Biologicals, 10th ed. Vol. 1. ILO.

Kaiser KLE, Oliver BG (1976) Analytical Chemistry, 48: 2207

NIOSH (1977) Manual of Analytical Methods, 2nd ed. CRC Press, Inc.

NIOSH (1979a) Revised Recommended Chloroform Standard. US Department of Health Education and Welfare.

NIOSH (1979b) Occupational Exposure to Chloroform. Criteria for a Recommended Standard. HEW Publication No. (NIOSH) 75-114. US Department of Health, Education and Welfare.

Pape BE (1977) Journal of Analytical Toxicology, 1: 46

Peoples AJ et al., (1979) Bulletin of Environmental Contamination and Toxicology, 23: 244

Pereira WE, Hughes BA (980) Journal of the American Water Works

Association, 72: 220

Piet GJ et al., (1978) Analytical Letters 11, pt.A: 437

Ploder I (1974) Deutsche Lebensmittel Rundschau, 70: 401

Pohl RL (1979) Reviews in Biochemical Toxicology, 1: 79

Ross RH et al., Environmental and Health Aspects of Selected Organohalide Compounds: An Information Overview. Oak Ridge National La., July 1978

Royal Society of Chemistry (1986) CEC. Organo-chlorine Solvents. ECSC-EEC-EAEC, Brussels-Luxembourg

Sax NI, (1984) Dangerous Properties of Industrial Materials. 6th ed., Van Nostrand Reinhold Co.

Simmonds PG, Kerns E (1979) Journal of Chromatography, 186: 785

Storms WW (1973) JAMA, 225:160

Waters R. Chloroform - A Study after 100 Years. University of Wisconsin Press, 1951

Winslow SG, Gerstner HB (1978) Drug and Chemical Toxicology, 1: 259

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