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REVIEW ARTICLE

IRRITANT COMPOUNDS: MILITARY RESPIRATORY IRRITANTS. PART I. LACRIMATORS

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Summary

World War I was a conflict where chemical warfare was first used on a massive scale. The earliest chemical attack occurred on the Western Front in October 1914 in Neuve Chapelle, but its effects were so minimal that the Allies learned about it only after the war from German documents. The attack in the Bolimow area, carried out by the Germans against the Russian army with artillery shells containing gas T (xylyl and benzyl bromides), was therefore the first attack on a massive scale recorded on the victim side. The attack, which occurred after it, made it possible to obtain some tactical success, but without a strategic breakthrough. Some of the later German attacks on the Eastern Front where chlorine was used proved to be more effective, but despite many victims there was not any major strategic success achieved. The Russians did not take attempts to use chemical weapons in the World War I.

Key words: respiratory irritants; irritant gases; chemical warfare agents; riot control agents; World War I

INTRODUCTION

Respiratory irritants are substances which can cause inflammation or other adverse reactions in the respiratory system (lungs, nose, mouth, larynx and trachea) after being inhaled. Depending on the type and amount of irritant gas inhaled, victims can experience symptoms ranging from minor respiratory discomfort to acute airway and lung injury and even death. The lungs are susceptible to many airborne irritants. A common response cascade to a variety of irritant gases includes inflammation, edema and epithelial sloughing which, left untreated, can result in scar formation and pulmonary and airway remodeling. There are hundreds of substances that can pollute air and harm lungs. Examples of respiratory irritants include, for example, chlorine, amonium, ozone, sulphur dioxide or nitrogen oxides (Patocka and Kuca, 2014). A special group of respiratory irritants finds use as chemical warfare agents that irritate airways. Many of them were deployed as chemical warfare agents on the front lines of the World War I (WWI) (Bajgar et al., 2009). Some of them have become a permanent part of chemical weapons

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of the armies of many countries (Patočka et al., 2004).

At present some of them are used as incapacitating chemicals as a new category of weapons. These are so-called ''non-lethal'' weapons, which are able to temporarily disable personnel from combat action (preferably without permanent consequences to their health, to the operation of other non-destructive combat material, or to their tactical and technical characteristics), and to protect the environment without limiting desired negative consequences to the enemy's national economy (Středa a Patočka, 2014). Nowadays, some irritating substances are used as so-called riot control agents by police, military, or other security forces to control, disperse, and arrest persons who are involved in a riot, demonstration, or protest. At present, only three agents are likely to be deployed: 1-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS), and dibenz[b,f]-1,4-oxazepine (CR) (Olajos and Stopford, 2004; Schep et al., 2013).

HISTORY

Irritating substances used in the past as chemical warfare agents belong to the category of incapacitating and debilitating substances, which complicate or disable affected combat operations. It is a common feature that, under normal conditions of use, they cause temporary incapacitation, but do not kill or cause grievous bodily harm (Kuča and Pohanka, 2010).

First irritant compounds were allegedly used by Marcus Fulvius against the Ambracians in the second century BC. The Byzantines apparently knew of the efficacy of using irritant substances to harass the enemy. Greek historian Plutarchos described a Roman general who used an irritant agent cloud in Spain to drive the enemy out of concealment in caves (Robinson, 1971).

Modern military use of irritants probably began in the 1910–1914 period, when ethyl bromacetate was employed against criminals by French police. At the beginning of WWI, some of these former policemen, who were then in the French army, began to use some of these munitions on the battlefield with some degree of success. The Battle of Bolimów was the first large-scale attempt by the Germans to use poison gas. The attack in the Bolimow area was carried out by the Germans against the Russian army with artillery shells containing gas xylyl and benzyl bromides.

On the battlefield of WWI, irritants occurred in the second month of the war and marked the mass use of chemical weapons, launched by Germany on the 22nd April 1915 on the front at Ypres, Belgium. The used irritant was chlorine gas and the date of the first gas attack is considered to be the begining of the use of chemical weapons in modern warfare (Patočka and Měrka, 2005; Ivanov, 2013). During World WWI, a lot of different compounds were tried for their irritant effects, usually without much success. In terms of their physiological effects, these substances can be divided into two large groups: Irritants with tear predominant effect (lacrimators) and irritants with a predominant effect on the upper respiratory system (sternites or sternutators) (Jackson, 1935). Lacrimators are the main focus of this article. These tear gases were fed into various kinds of artillery shells.

LACRIMATORS

Lacrimators are known irritants with a tear gas canister predominant effect. Lacrimators were first used in combat drugs. The very first ingredient was ethyl bromoacetate, seeded by Frenchmen in August 1914. Paris police was the first one in the world to be armed with rifle gas grenades, which were filled with ethyl bromoacetate. Shortly after the outbreak of war, 30,000 of these shells were moved to the battlefield. Gradually, a large amount of ammunition filled with various irritants was deployed on the battlefields of the WWI. During WWI, more than 30 different compounds were tried for their irritant effects, usually without much success. They are listed in Table 1 which shows a wide range of practically used substances which, for their easy availability, can also be misused by terrorists today (Larsen, 2001). In the war these substances cannot bring much success, but for terrorist use they can be very useful. It will be useful to provide more detailed information about these irritants.

Ethyl bromoacetate

Ethyl 2-bromoacetate ($CH_2BrCOOC_2H_5$, CAS Registry Number 105-36-2) is the ethyl ester of bromoacetic acid. This colorless to yellow liquid is poorly water soluble substance of density 1.51 g.cm^{-3},

Table 1. Irritant Chemical Agents with Tear Predominant Effect (Lacrimators) Used in World War I in Chronological Order *

Chemical name	Made in	Year of deployment on the front
Ethyl bromacetate	France	August 1914
Dianisidine chlorosulfonate	Germany	November 1914
Chloroacetone [1]	France	November 1914
Xylyl bromide [2]	Germany	January 1915
Benzyl bromide	Germany	March 1915
Methyl chlorosulfonate	Germany	June 1915
Methyl chlorocarbonate	Germany	June 1915
Ethyl chlorosulfonate	Germany	June 1915
Chloromethyl chlorocarbonate	Germany	June 1915
Dichloromethyl chlorocarbonate	Germany	June 1915
Bromoacetone [3]	Germany	June 1915
Bromo methyl ethyl ketone	Germany	July 1915
Iodoacetone	France	August 1915
Dimethyl sulfate		August 1915
Ethyl iodoacetate		September 1915
Benzyl iodide	Germany	November 1915
Benzyl chloride		November 1915
Acrolein [4]		December 1915
o-Nitrobenzyl chloride		December 1915
Ethyl chlorosulfonate	France	December 1915
Chlorpicrin [5]	Russia	1916
Thiophosgene	France	1918
Bromobenzyl cyanide [6]	France, Germany	July 1918
Chloroacetophenone		1918

* The table has been compiled based on information from Tuorinsky SD (ed.). Medical Aspects of Chemical Warfare, 2nd edition, Tuorinsky SD. (Ed), Office of the Surgeon General, TMM Publications, Washington, DC 2008. p. 339.

[1] In Germany it was known as A-Stoff, in France as Tonite
[2] In Germany it was known as T-Stoff
[3] In Germany it was known as B-Stoff, in France as Martonite, and BA in the United States
[4] In France it was known as Papite
[5] In Germany it was known as Klop, in France as Aquinite, and PS in the United States
[6] In France it was known as Camite, in Great Britain as BBC, and in the United States as CA

with m.p. -38 °C and b.p. 158 °C (Lide, 1998-1999). The log P = 1.12 and water solubility is 7.02 g/L. It is a lacrimator with fruity, pungent odour (Royer and Gainet, 1973). Vapors are irritant to all mucous membranes, esp. to eyes, and are unbearable for more than a min at concentration of 8 ppm in air (Lewis, 1996a).

Ethyl bromacetate is also a highly toxic alkylating agent and may be fatal if inhaled. This compound, administered s.c. to female ICR/HA swiss mice, induced sarcomas at injection site (Van Duuren et al., 1974). In WWI, ethyl bromoacetate was used as a lachrymatory agent and a tear gas agent for chemical warfare under the German code Weisskreuz (White Cross), and later as odorant or warning agent in odorless, toxic gases. It is listed by the World Health Organization as a riot control agent (Olajos and Stopfors, 2004).

Chloroacetone

Monochloroacetone, chloropropanone, halogenated ketone with the formula CH_3COCH_2Cl, CAS Registry Number 78-95-5, is a colourless liquid with a pungent odour. This compound having a density of 1.123 $g.cm^{-3}$ is sparingly soluble in water (10 g/100 ml) and miscible with alcohol, ether and chloroform (log P is 0.020). Its m.p. are -44.5 °C and b.p. 119 °C, respectively. Chloroacetone is an unstable compound, on exposure to light it turns to a dark yellow-amber colour. Chloroacetone was introduced in 1914 as a war gas, and presently it has a number of uses as a chemical intermediate. Apart from its biological properties as a lacrimator and vesicant, it is not a well-studied compound toxicologically (Sargent et al., 1986).

Acute toxicity (LD_{50}) of chloroacetone in mouse after oral (127 mg/kg) and intraperitoneal (92 mg/kg) application, in rat after oral (100 mg/kg) and intraperetoneal (80 mg/kg) application, and in rabbit (141 mg/kg) for skin application, were published by Sargent et al. (1986). Lethal concentration of chloroacetone in rat for inhalation is 262 ppm for 1 hour and a low odour treshold in human is 0.02 ppm (O'Neil, 2006).

Chronic exposure or carcinogenicity in dermal application of chloracetone to stock mice in 183 days had no tumorigenic effects, but 24 applications to albino mice, 0.2 mL, 0.3% in acetone (promotion with croton oil, 0.2 mL, 0.3% in acetone, 20 week), in 365 days resulted in 44/19 papillomas, 10/20 papillomas in controls (Searle, 1976). Chloroacetone genotoxicity has been tested for mutagenic potential and results were negative in five strains of Salmonella (Merrick et al., 1987).

Xylyl bromide

Xylyl bromide, a mixture of ortho-. meta-, and para-isomers , α-bromo-xylenes (CH_3-C_6H4)-CH_2Br, CAS Registry Number 104-81-4) is a clear liquid with an aromatic odour which is used as a tear gas and for production of other organic chemicals. A liquid of m.p. 38 °C and b.p. 218-220 °C with specific density 1.324 $g.cm^{-3}$, is soluble in ether, chloroform (Budavari, 1996) and ethanol (Lide, 1998-1999). This compound, manufactured by bromination of xylene, is a strong lacrimator and irritant (Grant, 1986) and is very toxic by ingestion and inhalation (Hawley, 1977). Occupational exposure to xylyl bromide may occur through inhalation and dermal contact with this compound at workplaces where p-xylyl bromide is produced or used (Lewis, 1997). The p-xylyl bromide is an important chemical raw material for the preparation of a number of important products.

Vapor-phase p-xylyl bromide will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 4.3 days. Due to the rapid rate of reaction of p-xylyl bromide in water, volatilization from water surfaces and bioconcentration in aquatic organisms are not expected to be important fate processes (Lucas, 1984).

Benzyl bromide

Benzyl bromide, or α-bromotoluene ($C_6H_5CH_2Br$, CAS Registry Number 100-39-0), is an organic compound consisting of a benzene ring substituted with a bromomethyl group. It can be prepared by the bromination of toluene at room temperature, using manganese oxide as a heterogeneous catalyst. It is a colorless to yellow up to light brown, clear, liquid with an unpleasant odour of m.p. -3.0 °C and of b.p. 201 °C, which is used to make foaming agents and other organic chemicals, that is decomposed slowly in water (Prager, 1996). This compound is soluble in benzene and tertrachlormethane, miscible in ethanol and ether and little soluble in water – only 385 mg/mL (P = 2.92).

Benzyl bromide is a strong lacrimator and is also intensely irritating to skin and mucous membranes. Because of these properties, it has been used as a war gas. The attack in the Bolimow area, carried out by the Germans against the Russian army with artillery shells containing gas T (xylyl and benzyl bromides), was the first attack on a massive scale recorded on the victim side (Ivanov, 2013). Benzyl bromide may cause pulmonary edema and high concentrations can cause CNS depression. Skin contact can cause redness and pain. It may be harmful if ingested, absorbed through skin, or inhaled. Genotoxicity of benzyl bromide has been tested for mutagenic potential and results were negative in five strains from six strains of Salmonella (Zeigleret al., 1992).

Methyl chlorosulfonate

Methyl chlorosulfonate, methyl chlorosulfate, chloridosulfuric acid methyl ester ($ClSO_3CH_3$, CAS Registry Number 812-01-1) is a liquid of density

1.557 g.cm^{-3} and b.p. 132 °C. Methyl chlorosulfonate is prepared by reacting methylene chloride with sulfur trioxide, and the compound is used in organic synthetic chemistry (Geering, 1987). Methyl chlorosulfonate as a warfare agent was not successful on the front lines of WW1 (Szinicz, 2005).

Methyl chlorocarbonate

Methyl chlorocarbonate, methyl ester of chloroformic acid, also known as methyl chloroformate ($ClCOOCH_3$, CAS Register Number 79-22-1) is an oily liquid (density 1.223 g.cm^{-3}, b.p. 70-72 °C, log P = 0.140) with a colour that is anywhere from yellow to colorless. It is also known for its pungent odour. The compound is very toxic by inhalation and toxic by skin contact and ingestion (Sax and Lewis, 1987). Acute toxicity (LD50) in rabbit at skin application is 7120 mg/kg and in rat at inhalation 88 ppm/1 hr (Vernot et al., 1977) and in rat at oral application <0.05 g/kg (Clayton and Clayton, 1981-1982). This corrosive substance causes burns, lacrimation and may cause lung edema after inhalation of high concentrations. Humans exposed to methyl chlorocarbonate have experienced respiratory tract and eye irritation, even persisting after cessation of exposure. A concentration of 10 ppm has caused lacrimation and a concentration of 190 ppm (1 mg/liter) has been lethal in 10 minutes (Clayton and Clayton, 1981-1982). Methyl chloroformate, if heated, releases phosgene and produces toxic, corrosive fumes if it comes in contact with water.

Methyl chlorocarbonate is used in organic synthesis for the introduction of the methoxycarbonyl functionality to a suitable nucleophile and in analytical chemistry to derivatization of some analytes (Chen et al., 2010; Mudiam et al., 2013). Methyl chloroformate is used to make pesticides, pharmaceuticals and other chemicals and also as a solvent in the photographic industry.

In 1972 a case of intoxication of a chemical production worker by methyl chlorocarbonate was described by Schuckmann (1972). The exposure was limited to 2-3 inhalations of the atmosphere surrounding a leaking piece of equipment. The observed symptoms differed markedly from the limited reports on this material or the chemically related phosgene. After brief initial irritation the patient was discharged without complaints 6 hr after the accident, but massive symptoms reoccurred after a latency period of 36 hr, characterized by heavy cough, dyspnea and light lip cyanosis. Symptoms and improvement, with relapse in wavelike fashion, becoming more severe in the morning hours and regressing in the evening, occurred during a 9 day period, eventually followed by full recovery. These unexplained phenomena suggest prolonged observation of exposed persons.

Dichloromethyl chlorocarbonate

Dichloromethyl chlorocarbonate, dichloromethyl carbonochloridate, dichloromethyl chloroformate ($ClCOOCHCl_2$, CAS Registry Number 22128-63-8) is an oily liquid (density 1.560 g.cm^{-3}, b.p. 110.5 °C) insoluble in water (Ho et al., 2007). Vapors of dichloromethyl chlorocarbonate form explosive mixtures with air which are heavier than air. They will spread along ground and collect in low or confined areas. Vapors may travel to source of ignition and flash back. Substance will react with water releasing flammable, toxic or corrosive gases and runoff (ChemSink).

Under the name „palite“, a French term for monochloromethyl chlorocarbonate mixed with stannic chloride or with dichloromethyl chlorocarbonate, this compound was used as not a very successful warfare agent (Marrs et al., 2007). No reliable toxicological data are available.

Bromoacetone

Bromoacetone, 1-bromo-2-propanone(CH_3COCH_2Br, CAS Registry Number 598-31-2) is a volatile colorless liquid that turns violet and then black on standing, having a density of 1.634 g.cm^{-3}. Bromoacetone has been prepared by the bromination of acetone under a variety of conditions (Lewis, 2007). Its freezing and boiling points are, respectively, of -36.5 °C and 138 °C. Bromoacetone decomposes to hydrogen bromide and a dark colored resinous solid in the presence of sunlight (O'Neil, 2006).

Bromoacetone is toxic by inhalation and skin contact (Lewis, 2007). When bromoacetone was evaluated for acute inhalation toxicity in rats, all animals exhibited tearing and salivation, followed by nasal discharge and labored breathing. Post-exposure clinical responses during 14-day observation included wheezing, severe dyspnea, bloody nasal discharge, and weight loss.

Human lethality data for bromoacetone were not located. In experiment,six human volunteers (age and sex not stated) were self-exposed to 0.1 ppm or 1.0 ppm (analytical bromoacetone to investigate

acute irritative effects and odor (Dow Chemical, 1968). Exposure duration was not stated, however, it appears to have been no more than a few seconds. The eye irritation test was accomplished by passing the prepared vapor sample from a Saran bag into a modified chemical workers goggle worn by the subject. The odor test was accomplished by sniffing the gas sample from the exposure chamber or gas sampling bag containing the gas. All 6 subjects reported considerable occular irritation at 1.0 ppm. No other information was provided.

Human LCLo (Lethal Concentration Low) at inhalation is 572 ppm/10min (O'Neil, 2006). Permanent dense opacification of cornea has resulted from splashing liquid bromoacetone in the eye. A relatively minor injury has occurred in a case in which only a few fine droplets came in contact with an eye. Spots of gray opacity and necrosis appeared in corneal epithelium, but in a few days the eye recovered completely (Grant, 1986).

Bromo methyl ethyl ketone

Bromo methyl ethyl ketone, 1-Bromo-2-butanone ($CH_3CH_2COCH_2Br$, CAS Registry Number 816-40-0) is a colorless to light yellow liquid having a density of 1.479 $g.cm^{-3}$ with calculated P = 1.206 (Catch et al., 1948). All bromomethyl ketones are highly lacrimatory and are skin irritants (Lide and Milne, 1995).

At present bromo methyl ethyl ketone is used in organic synthesis and employed as a reagent for aromatic bromination with sodium hydride in DMSO. Also it is used in a microwave-assisted preparation of fused heterocycles (Owens et al., 2015).

Dimethyl sulfate

Dimethyl sulfate (DMS, $CH_3O\text{-}SO_2\text{-}OCH_3$, CAS Register Number 77-78-1) is a colorless oily liquid with a slight onion-like odour (density 1.386 $g.cm^{-3}$, m.p. – 32C°C, b.p. 188 °C). In the past, dimethyl sulfate was used as a chemical warfare agent, at present it is widely used in chemical and biochemical laboratories. DMS is also used in chemical plants and as a highly toxic compound it may therefore represent an occupational problem (Schettgen et al., 2004).

DMS is an extremely hazardous substance (Hamilton and Hardy, 1974). Its main effects of vapor exposure are irritation and erythema of eyes progressing to lacrimation and blepharospasms. Corneal ulceration and severe inflammation of the eyes and eyelids with photophobia are commonly reported. These symptoms generally resolve satisfactorily, though irreversible loss of vision has been reported. The eye effects are probably attributable to the metabolism of dimethyl sulfate to methanol and sulfuric acid. Cough, hoarseness, and edema of tongue, lips, larynx, and lung occur later. Ingestion or direct contact with mucous membranes cause corrosions equivalent to that from sulfuric acid. After absorption, pulmonary edema and injury to liver and kidneys (Dreisbach, 1987) occur. Liquid DMS produces severe blistering and necrosis of skin. According to Patty (1963), soldiers gassed with dimethyl sulfate during WWI were noted to have analgesia.

DMS is classified as a hepatotoxin. Symptoms of hepatic disease include malaise, lethargy, nausea, vomiting, pruritus, right upper quadrant pain, and anorexia. Complications of hepatic failure are portal hypertension, edema, spider angiomata, upper gastrointestinal bleeding, encephalopathy, electrolyte imbalance and renal failure (Ellenhorn and Barceloux, 1988). DMS is probably carcinogenic to humans (Group 2A) (Zheng et al., 2009).

DMS is highly toxic for humans, particularly to the respiratory tract. Many cases of accidental acute intoxication from the inhalation of DMS in industrial workers were reported (Ip et al., 1989; Kinoshita et al., 1992; Schettgen et al., 2004; Wang et al., 2011). Signs and symptoms uniformly found after each exposure began with headache and giddiness with burning of the eyes, reaching maximal intensity in 2 to 10 hours after the first eye effects. The condition becomes progressively worse with painful, reddened eyes, followed by photophobia, irritation of nose and throat, hoarseness and loss of voice, cough, difficult breathing and swallowing (Wu et al., 2007). Finally symptoms are vomiting, diarrhea, and scalding urination. Painful and difficult urination persists for 3 to 4 days, and congestion of mucous membranes and edema of the larynx may persist for 2 weeks. In some cases examined 6 years later, there was some impairment of liver function and reduction in the visual fields for various colors. When death occurs, the signs indicate circulatory failure (Aghabiklooei et al., 2010).

Ethyl iodoacetate

Ethyl iodoacetate ($ICH_2COOCH_2CH_3$, CAS Register Number 623-48-3) is a colorless oily liquid

(density 1.808 g.cm^{-3}, b.p. 179-180 °C, log P = 1.620). At present ethyl iodoacetate shows limited use in organic synthesis (Cozzi et al., 2008). Ethyl iodoacetate is a lacrimator that reacts with simple thiol groups and thus inhibits almost all the enzymes generally considered to be of a thiol nature (Mackworth, 1948). It is as toxic as ethyl bromoacetate and more toxic than ethyl chloroacetate and ethyl fluoroacetate (Dawson et al., 2011).

Acute toxicity (LD_{50}) in mouse was 45 mg/kg at intraperitoneal and 50 mg/kg at oral administration and the same values for rat was 10 mg/kg and 50 mg/kg, respectively (TOXNET). More toxicological data are not available.

Ethyl chlorosulfonate

Ethyl chlorosulfonate (ethylchloro sulfate, $CH_3CH_2OSO_2Cl$, CAS Registry Number 625-01-4) is a liquid with b.p. of 152.5 °C and log P = 2.210. This warfare agent was used in WWI as a lacrimator only in small quantities and information about its use is insufficient. Information about its toxicity is also lacking (Szinicz, 2005).

Benzyl iodide

Benzyl iodide, α-iodo toluene, iodo methyl benzene ($C_6H_5CH_2I$, CAS Registry Number 620-05-3) is low-melting crystals or a colorless liquid, with melting point 24.5 °C, b. p. 83-84 °C (3 mmHg) and density of 1.750 g.cm^{-3}, practically insoluble in water, only 53.7 mg/L (log P = 3.300). It is toxic by ingestion, inhalation and skin absorption and very irritating to skin and eyes (Alarie et al., 1998). Acute inhalation toxicity of benzyl iodide (RD_{50}) is 4.3ppm (Dudek et al., 1992). More toxicological data are not available.

o-Nitrobenzyl chloride

o-Nitrobenzyl chloride (2-nitro benzyl chloride, O_2N-C_6H_4-CH_2Cl, CAS Registry Number 612-23-7) is liquid or palle yellow crystals, insoluble in water (log P = 2.610) and thermalle instable (Cardillo and Girelli, 1984), having a density of 1.556 g.cm^{-3}, m.p. 46-48 °C and b.p. 127-133 °C.

This halogenated aromatic nitro compound is a hazardous toxic lacrimator which causes irritation on contact (Boa and Jenkins, 2001). This compound was positive in many mutagenicity studies (Shimizu and Yano, 1986; Kawai et al., 1987). Its decomposition products are also hazardous. No other information was provided.

Benzyl chloride

Benzyl chloride (C_6H_5-CH_2Cl, CAS Registry Number 100-44-7) is a colorless to slightly yellow liquid with a pungent, aromatic odour. This compound is an extreme irritant to skin, eyes, and mucous membranes. Symptomatology may include severe irritation of the upper respiratory tract, conjuctivitis, dizziness, weakness, headache, tremors in eyelids and fingers, increased bilirubin in blood, and decrease in number of leukocytes (Brondeau et al., 1990). Benzyl chloride causes lung damage pulmonary edema, permanent eye damage (Mirzayans et al., 1982), and CNS depression are all possible from severe exposure (De Ceaurriz et al., 1982).

There is only limited evidence in animals and this prevents benzyl chloride from being classified for its carcinogenicity to humans (Yasuko et al., 1975; Hemminki et al., 1983; Lijinsky, 1986). Findings of Fall et al. (2007) suggest that benzyl chloride may show greater mutagenic activity in the gaseous phase.

Acrolein

Acrolein (propenal, acrylic aldehyde, allyl aldehyde, H_2C=CHCHO, CAS Registry Number 107-02-8) is the simplest unsaturated aldehyde. It is produced industrially from propylene and mainly used as a biocide and a building block to other chemical compounds, such as the amino acid methionine. A number of useful compounds are made from acrolein, exploiting its bifunctionality. Acrolein is a volatile liquid having m.p. -8.7 °C and b.p. 52.6 °C with log P = -0.01.

Acrolein is a colourless liquid with a piercing, disagreeable, acrid smell, having a density of 0.839 g.cm^{-3}, m.p. -88 °C and b.p. 53 °C. Acrolein is very soluble in water. The smell of burnt fat is caused by glycerol breaking down into acrolein (Andreas et al., 2012). It is formed from carbohydrates, vegetable oils and animal fats, amino acids during heating of foods, and by combustion of petroleum fuels and biodiesel and represents health risk (Klaus et al., 2011).

Acrolein vapor may cause eye, nasal and respiratory tract irritations in low level exposure. A decrease in breathing rate was reported by volunteers acutely exposed to 0.3 ppm of acrolein. At a similar level,

mild nasal epithelial dysplasia, necrosis, and focal basal cell metaplasia have been observed in rats, Acrolein induces the respiratory, ocular, and gastrointestinal irritations by inducing the release of peptides in nerve terminals innervating these systems (Faroon et al., 2008).

Acrolein is highly toxic, inducing irritation of the respiratory and gastrointestinal tracts and central nervous system depression at relatively low levels. Acute LD_{50}s and LC_{50}s are low. Levels are 7-46 mg/kg and 18-750 mg/m^3, respectively, in rats; aquatic organisms are affected above 11.4 micro-grams/L (Ghilarducci DP, Tjeerdema, 1885). LDLo for cat administered intravenously was 15 mg/kg (Skog, 1952) and LC_{50} for mouse at 6 hours inhalation was 66 ppm (Philippin et al., 1970). Acrolein is cytotoxic and degenerative histopathological lesions have occurred consistently at the respiratory tract (Yadav et al., 2013). This is consistent with the results of toxicokinetic studies in rodents and dogs, in which there has been a high degree of retention of inhaled acrolein at the site of contact (Feron et al., 1978). Species-related differences in sensitivity to acrolein have been observed, with adverse effects on the respiratory tract of dogs and rats at lowest concentrations (Lyon et al., 1970; Cassee et al., 1996).

Ethyl chlorosulfonate

Ethyl chlorosulfonate, ethyl chlorosulfate, chloridosulfuric acid ethyl ester ($ClSO_3$ CH_2CH_3, CAS Registry Number 625-01-4) is a liquid of density 1.441 g.cm^{-3} and b.p. 153.9 °C. Ethyl chlorosulfonate is prepared by reacting ethylene chloride with sulfur trioxide, and the compound is used in organic synthetic chemistry (Geering, 1987). Ethyl chlorosulfonate was used as lacrimator in WW1 (Jackson and Jackson, 1935) but as a warfare agent it was not successful on the front lines (Szinicz, 2005).

Chloropicrin

Chloropicrin (nitrochloroform, trichloronitromethane, Cl_3CNO_2), CAS Registry Number 76-06-2) is a chemical compound currently used as a broad-spectrum antimicrobial, fungicide, herbicide, insecticide, and nematicide but in 1915 it was manufactured in Russia to be used in large quantities during WWI and was stockpiled during WWII. However, it is no longer authorized for military use.

Pure chloropicrin is a colorless to faint-yellow, oily volatile liquid with an intensely irritating odor, with a m.p. -69 °C and b. p. of 112 °C. Chloropicrin is sparingly soluble in water with solubility of 1620 mg/L at 25 °C. This compound is an irritant with characteristics of a tear gas. Chloropicrin has an intensely irritating odor. Inhalation of 1 ppm causes eye irritation and can warn of exposure. The value of human LCLo inhalation was 2.000 mg/m^3 (Deichman, 1969). Chloropicrin is mutagenic (Kawai et al., 1987).

Thiophosgene

Thiophosgene (thiocarbonyl chloride, $CSCl_2$) CAS Registry Number 463-71-8 is a red liquid of a sharp choking odor with a density of 1.50 g.cm^{-3} and b.p. of 70-75 °C. It is a polar organic solvent decomposing by water. Thiophosgene hydrolyzes (more slowly than phosgene) into CO_2, H_2S, and HCl. At present thiophosgene is used as a reactant in organic synthetis (Sharma, 1978).

Thiophosgene is a corrosive lacrimator which can cause severe burns and delayed pulmonary edema. Its acute toxicity (LD_{50}) in rat at oral application was 929 mg/kg (Marhold, 1972). Thiophosgene was mutagenic when tested using *Salmonella typhimurium* and its LD_{50} in mouse at intravenous application was 100 mg/kg and in rat at oral application 929 mg/kg (Lewis, 1996b).

Bromobenzyl cyanide

Bromobenzyl cyanide (α-bromobenzyl cyanide, bromophenyl nitrile, $C_6H_5CHBrCN$, CAS Registry Number 5798-79-8) is in pure form pale yellow crystals with an odor of soured fruit and m.p. 29 °C. In impure form it is an oily brown liquid used as a war gas and irritant gas for law enforcement. Bromobenzyl cyanide is extremely toxic and exposure to high concentrations may be fatal. Lowest irritant concetration was 0.15 mg/m^3 and intolerable concentration was 0.8 mg/m^3 (Clayton and Clayton, 1981-1982). The concentration of 109 ppm is lethal to humans in 5 hours (Grant, 1974).

Chloroacetophenone

Chloroacetophenone (2-chloro-1-phenylethanone, 2-chloroacetophenone, CAS Registry Number 532-27-4) is a colorless to white crystalline solid. It may appear as a blue-white cloud at the point of release. Cloracetophenone is a strong lacrimator or better irritant incapacitant (Potter, 1982) and under the name CN it became an important riot control agent (Blain, 2003).

CONCLUSIONS

Respiratory irritant substances which can cause inflammation or other adverse reactions in the respiratory system (lungs, nose, mouth, larynx and trachea) after being inhaled were deployed as chemical warfare agents on the front lines of the WWI. Some of them have become a permanent part of the chemical weapons the armies of many countries. However, their current importance for chemical warfare is small. Yet, they can be misused as a weapon in local wars in the position of incapacitaning chemicals or as a tool of terrorism. Some of them can be used as riot control gases.

During the last three years, various international forums, above all the experts' meetings (two organized by the International Committee of the Red Cross, ICRC, in the years 2010 and 2012, one organized by the organisation VERIFIN in Spiez in the year 2011) have held discussions about toxic chemicals applicable for law enforcement purposes. These discussions were focused on new toxic chemicals with an incapacitating effect which could be developed, produced or used in consequence of advances in science and technology. This could obscure the distinction between use for law enforcement purposes and use as a method of warfare and so undermine the purpose and objectives of the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction (Středa and Patočka, 2014).

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