Chapter 13

RIOT CONTROL AGENTS

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INTRODUCTION

The 1993 Chemical Weapons Convention treaty defines riot control agents (RCAs) as agents that can rapidly produce sensory irritation or disabling physical effects in humans that disappear within a short time following termination of exposure.[1] More specifically, these are chemical agents that are designed to cause temporary incapacitation of the individual through intense irritation of tissues and the creation of a strong sensation of discomfort, including difficulty breathing and pain, without causing long-term disability or death. These disabling physiological effects occur when RCAs come into contact with the sensory nerve receptors at the site of contamination, resulting in local pain and discomfort with associated reflexes.

RCAs include chemicals from the following pharmacological classes: irritants, lachrymators, sternutators, emetics, sedatives, hypnotics, serotonin antagonists, hypotensives, thermoregulatory disruptors, nauseants, vision disruptors, neuromuscular blockers, and malodorous substances.[2] They are considered harassing agents, nonlethal or less than lethal agents, and although not gases, they are usually referred to as tear gas.[3] RCAs are relatively safe to use, especially when used in the open air, but have been known to cause death on occasion, particularly when used in close confines with inadequate ventilation or when the exposed individual was predisposed to cardiorespiratory compromise through disease or heavy intoxication with drugs or alcohol. Like other chemical agents, RCAs are designated with North Atlantic Treaty Organization (NATO) letter codes to label and help distinguish them. The agents covered in this chapter are those that have been used, or allegedly used, since World War II; their chemical names and respective NATO codes are *o*-chlorobenzylidene malononitrile (CS); oleoresin capsicum (OC); chloropicrin (PS); 1-chloroacetophenone (CN), diphenylaminearsine (DM), and dibenz*(b,f)*(1,4)oxazepine (CR).

Characteristics common to all of the agents discussed in this chapter are

- a rapid time of onset of effects (seconds to a few minutes);
- a relatively brief duration of effects (15–30 minutes) in most cases, once the exposed individual exits the contaminated area and is decontaminated (ie, the material is removed from the victim's clothing and skin); and
- a high safety ratio, that is, a relatively low dose of these agents is needed to cause tissue irritation or pain (effective dose or effective concentration), but a significantly larger dose is required to cause death (lethal dose or lethal concentration, LCt_{50}).[2–4]

This chapter will cover only RCAs that have been purposefully or allegedly used in recent history. Because of their prevalent use, CS and OC will be covered in greater detail than other agents.

Although the effects differ slightly among the various agents, all RCAs cause some form of eye irritation involving lacrimation and blepharospasm, which causes the eyes to close temporarily, rendering victims unable to see and dramatically reducing their ability to resist. PS, CN, CS, CR, DM, and OC also cause irritation to airways resulting in coughing, shortness of breath, and retching or vomiting.[3] DM in effective doses causes significant vomiting with resulting mental depression and malaise. These agents cause some degree of pain sensation either through irritation of peripheral nerve endings in tissue, such as the mucous membranes and skin (PS, CN, CS, CR), or by causing the sudden release of neurotransmitters, such as bradykinin or substance P, which signal the sensation of intense pain (OC).[2]

The reflex most associated with death from the inhalation exposure of irritants is the Kratschmer reflex, first reported in 1870 as the immediate response of apnea or cessation of respiration in rabbits following exposure to chemical irritants such as chloroform and carbon dioxide.[5] The response is a protective reflex or defense mechanism to prevent or reduce the amount of noxious chemical reaching the lower respiratory tract and maintain homeostasis. Accompanied by bradycardia and a biphasic fall and rise in aortic blood pressure, the reflex is mediated by the olfactory (I), trigeminal (V), and glossopharyngeal (IX) cranial nerves. It has also occurred in rodent and canine experiments following exposure to volatile solvents and was demonstrated to occur in humans.[6] The cardiopulmonary receptors involved in the reflex prevent the absorption and distribution of the inhaled irritant to the vital organs, as well as facilitating the expulsion of the irritant, and the extracardiopulmonary mechanisms promote metabolism and excretion of the absorbed chemical. These effects have been described by Aviado and Salem and by Aviado and Aviado.[7–9] During apnea or cessation of respiration, blood levels of carbon dioxide increase and drive the respiratory center to restart breathing. Individuals with compromised immune systems, nervous system depression as a result of alcohol or illicit drug consumption, or a combination of these, may not be able to restart respiration and die from asphyxia. The Kratschmer reflex may be responsible in part for some in-custody deaths attributed by law enforcement agencies to positional asphyxia following the initial use of pepper sprays in the United States in the early 1990s.[2]

Police departments throughout the world commonly use RCAs, either individually or in solutions combining several agents (OC, pelargonyl vanillylamide [PAVA or nonivamide], CS, CN, CR, and malodorous substances), as an alternative to deadly force for individual protection, subduing unruly felons, crowd control during civil disturbances, or rescuing hostages. RCAs are also regularly used by the military for mask confidence training (CS) and by military police for individual protection (OC). Because of their frequent use during peacetime operations, RCAs are repeatedly scrutinized for safety and appropriateness.

RCAs are usually solids with low vapor pressure. They can be dispersed as fine powders or in solvents as jets or streams from spray cans, tanks or larger weapons, hand grenades, or mortar artillery munitions, and also as aerosols or smoke by pyrotechnic generators.[10]

HISTORY

Irritant compounds have been used throughout history. In the 2nd century BCE, Plutarch, the Roman historian, described a Roman general using an irritant cloud to drive an enemy from caves in Spain.[3] The Byzantines also used irritants to harass opposing forces. Chinese warriors and Japanese ninjas reportedly threw or blew ground cayenne pepper powder mixtures in the faces of their opponents to temporarily disable them. Japanese police once used a lacquer or brass box, known as the *metsubichi*, to blow pepper dust in the eyes of criminals trying to flee arrest.[11,12]

Use of RCAs by Europeans in the 20th century probably began before World War I when French police used ethylbromoacetate against criminals and gangs.[13] France used the agent on the battlefield in the early part of the war, with limited success, before Germany's first use of lethal chlorine, in Ypres, Belgium, on April 22, 1915.[3] Other tear gases used in World War I included acrolein (Papite); bromoacetone (BA, B-stoff); bromobenzyl cyanide (BBC, CA); chloroacetone (A-stoff); and xylylbromide (T-stoff). Ethylbromoacetone was the most widely used potent lacrimatory agent during the war.[14]

First synthesized around 1850, PS was known as "green cross" during World War I, when it was used as a harassing agent and lethal chemical along with the other lethal agents such as chlorine, phosgene, and trichloroethyl-chlorformate. PS is no longer used as an RCA because of its toxicity, but it is used in agriculture as a soil fumigant injected below the soil surface as an effective fungicide, insecticide, and nematicide.[15,16] In 2004 an accidental release of PS in a crowded central police office in Sofia, Bulgaria, sent 49 persons to the hospital with tearing and serious respiratory complaints.[17,18] DM, an arsenic-based compound, was developed for use in the latter part of World War I. It is a vomiting and sneezing (sternutator) agent and was used as an RCA after the war; however, it is currently considered obsolete.[4] Around the year 2000 Palestinian sources accused Israel of using a chemical agent compound, possibly DM, as an RCA, although this claim has never been substantiated.[19,20] CN was invented by a German chemist, Carl Graebe, in 1869 (although some sources indicate that it was originally synthesized in 1871 or 1881). CN was used as the RCA of choice from the latter part of the First World War through the 1950s, until it was replaced by the less toxic CS as the standard RCA in the United States.[3,21] Some countries still use CN as an RCA, and it is still found in some personal defense sprays. CS, synthesized in 1928,[3] in addition to its use as an RCA, is used for individual protection, sometimes in combination with CN, OC, or PAVA.[10] CR is believed to have been deployed initially in the 1970s by the British against prison rioters. It is not in use in the United States, but some countries use the agent for riot control and security.[22] OC was originally developed as an animal repellent and used by the US Postal Service in the 1960s. In the late 1980s it was endorsed by the Federal Bureau of Investigation as a chemical agent that would be effective in subduing people.[22,23] In the 1990s OC gained wide acceptance among US law enforcement personnel, including military police, as an alternative to Mace (Smith and Wesson, Springfield, Mass) for individual protection. It now comes in a variety of forms, from liquid to dry powder.[10,12]

The United States does not consider RCAs to be chemical warfare agents as defined by the Geneva Convention in 1925. The United States ratified the Geneva Gas Protocol in January 1975, interpreting it as prohibiting the first use of lethal chemicals, but not nonlethal agents or herbicides[3] (US forces were then using CS and Agent Orange in Vietnam). On April 18, 1975, President Gerald Ford signed Executive Order 11850 renouncing first use of RCAs in war, except in defensive military modes to save lives. The executive order did allow the use of these agents against rioting prisoners and civil disturbances, during rescue operations, for nuclear weapons security operations, and to protect convoys from terrorist attacks or in similar situations.[3,10] Under current policy, the secretary of defense must ensure that RCAs are not used in warfare unless there is advance presidential approval.[10]

CS (*O*-CHLOROBENZYLIDENE MALONONITRILE)

CS (also known as 2-chlorophenyl-methylenepropanedinitrile, β,β-dicyano-*o*-chlorostyrene, and 2-chlorobenzalmalononitrile) is the US military's most widely used RCA compound in operations and training. CS was first synthesized by British scientists Corson and Stoughton (hence its name) in 1928 by condensing aromatic aldehydes with malononitrile.[24] Corson and Stoughton showed CS to have an intense nasal (sneezing) and skin irritant effect and noted that exposure to it caused the "face to smart." This outcome can be minimized by wearing a protective mask, but may be temporarily intensified if the exposed area is rinsed with water.[24] These characteristics made CS a notable candidate for widespread adoption as a military incapacitant. However, CS wasn't readily accepted for this use until well after World War II, when it was learned that the effect of CS was less toxic but more potent than that of CN. As a result, the US Army Chemical Corps declared CS its standard military RCA on June 30, 1959.[25] See Table 13-1 for a summary of CS characteristics.

Other symptoms of CS exposure, which may be associated with bradykinin release, consist of irritation and a burning sensation of the eyes, nose, skin, and throat, resulting in the need for exposed individuals to close their eyes and hold their breath, quickly rendering them incapacitated.[26,27] Recent scientific investigations into the identification of CS-derived compounds and other thermal degradation products formed during the heat dispersion of CS have raised questions about the potential health risks associated with the use of high-temperature heat dispersion devices, particularly if used in enclosed spaces.[28–31] It is critical that CS be deployed in accordance with existing training guidance to minimize its potential health hazards.

Physical Characteristics and Deployment

Physical Characteristics

CS is a gray, crystalline solid with a pepper-like odor. Additional characteristics are a molecular mass of 188.6 d; molecular formula of $C_{10}H_5\ ClN_2$ (Figure 13-1); melting point of 95°C to 96°C; boiling point of 310°C to 315°C; low vapor pressure of 3.4×10^{-5} mm Hg at 20°C; slight solubility in water; solubility at 25°C in the organic solvents methylene chloride, acetone, ethyl acetate, benzene, and dioxane; and half-life of 14 minutes at pH 7.4 and 25°C. Dissolved CS is rapidly hydrolyzed to form *o*-chlorobenzaldehyde and malononitrile.[32]

Deployment

CS rapidly loses its effectiveness under normal environmental conditions, making it an ideal temporary incapacitant. The US Department of Defense created at least three variations of CS—CS1, CS2, and CSX—all of which are used today. CS1 is a micronized powder consisting of 95% CS and 5% silica aerogel designed to reduce agglomeration. CS2 is a siliconized microencapsulated form of CS1 comprised of 94% CS, 5% colloidal silica, and 1% hexamethyldisilizane, whose characteristics increase shelf life, resistance to degradation, and the ability to float on water, thus providing a means of restricting key terrain during military operations.[33] CSX is comprised of 1 g CS1 dissolved in 99 g trioctylphosphite, enabling dissemination as a liquid. CS powder is usually delivered as a component of an aerosol, solution, explosive device, or smoke.[34]

The mechanism of deployment typically involves the use of storage cylinders, mortars, artillery projectiles, grenades (Figures 13-2 and 13-3), cartridges, aircraft or vehicle-mounted dispensers, portable dispensers, or personal protection dispensers.[34] Regardless of the delivery mechanism, CS exposure causes almost immediate inflammation of the conjunctivae, tearing (lacrimation), pain, and involuntary closure of the eyes and lids (blepharospasm). Respiratory effects include sneezing, nasal discharge, and throat irritation, often accompanied by violent coughing. Continued CS exposure results in tightness of chest and general breathing difficulty. These effects resolve within minutes of removal from the exposure, and only moderate tearing and redness of the eyes remain 10 minutes after exposure.[35,36]

In addition to its use by the United States in Vietnam, during demonstrations and prison riots, and for military and law enforcement training,[36] CS was used by British police to quell riots in Londonderry in August 1969.[37,38] CS has an extensive mammalian toxicology database.[2]

Thermal Degradation Products

CS is commonly used as an RCA and chemical warfare agent simulant for training, in which law enforcement and military employees are routinely exposed to heated CS. Heat assists in the dispersion process by vaporizing the CS, which then condenses to form an aerosol. Heat dispersion of CS has the potential to form CS-derived compounds that have been the focus of many recent studies. Thermal dispersion of CS from a canister in an enclosed space was shown to

TABLE 13-1

CHARACTERISTICS OF CS AND OC

Properties	CS	OC
Molecular formula	$C_{10}H_5ClN_2$	$C_{18}H_{27}NO_3$
Former/current use	RCA/RCA	Food additive/Food additive, RCA
Physical state*	White crystalline solid.	Colorless solid
Odor	Pungent pepper-like	Pungent, irritating
Freezing or melting point	Melting point: 95°C–96°C	Freezing point: 65°C
Vapor pressure	0.00034 mm Hg at 20°C	1.5×10^{-7} mm Hg at 65°C (extrapolated)
Density:		
Vapor (relative to air)	6.5 times heavier (calculated)	10.5 times heavier (calculated)
Solid	Bulk: 0.24-0.26 g/cm^3 Crystal: 1.04 g/cm^3	Data not available
Solubility:		
In water	Insoluble in water	Solubility in water is 0.090 g at 37°C
In other solvents	Moderate in alcohol; good in organic solvents such as acetone, chloroform, methylene dichloride, ethyl acetate, and benzene	Soluble in alcohol, ether, oil, chloroform, aromatic solvents, hydrocarbons, ketones, and aqueous alkali
Hydrolysis products	Data not available	Alkaline hydrolysis yields vanillylamine and isomeric decenoic acid
Decontamination:		
Clothing	Stand in front of a fan or flap arms to remove dry powder, protect airway. Wash clothing after removal	Sticks to clothing if in liquid solution. If in powder form, remove dry powder. Wash clothing after removal
Skin	Copious soap and water; do not use oil-based lotions or bleach	Copious soap and water. Can also use alcohol, baby shampoo, or flush skin with vegetable oil followed by soap and water (not for OC/CS-CN mixtures); flush eyes with copious water or baby shampoo; use milk or ice packs to reduce pain
Equipment	Wash with soap and water	Wash with soap and water or place in sun to degrade
Persistency:		
In soil	Varies	Degrades with sun and moisture
On material	Varies	Degrades with sun and moisture
Skin and eye effects	Skin irritant; itching, stinging and erythema; may cause blistering and allergic contact dermatitis. Burning and irritation to eyes with lacrimation and accompanying blepharospasm	Causes sensation of intense pain and burning through the activation of the TRPV1 sensory neuron, causing release of substance P. May cause allergic dermatitis with excessive skin exposure. Lacrimation, redness, burning sensation in the eyes and blepharospasm
Respiratory effects	Salivation, coughing, choking, and a feeling of chest tightness. May cause reactive airway disease syndrome requiring medical intervention	Tingling sensation followed by coughing and decreased inhalation rates. Pain, vasodilation, and secretion can occur in the airways depending on the dose inhaled

*At standard temperature and pressure.
RCA: riot control agent
TPRV1: transient receptor potential, vallinoid subtype 1
Data sources: (1) Sidell F. Riot control agents. In: Sidell F, Takafuji E, Franz D, eds. *Medical Aspects of Chemical and Biological Warfare.* In: Zajtchuk R, Bellamy RF, eds. *Textbook of Military Medicine.* Washington, DC: Department of the Army, Office of The Surgeon General, Borden Institute; 1997: Chap 12. (2) US Department of the Army. *Potential Military Chemical/Biological Agents and Compounds, Multiservice Tactics, Techniques, and Procedures*. Washington, DC: DA; January 10, 2005. FM 3-11.9. (3) Somani SM, Romano JA Jr, eds. *Chemical Warfare Agents: Toxicity at Low Levels*. Boca Raton, Fla: CRC Press; 2001.

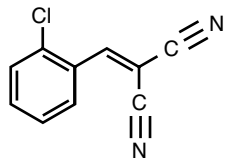

Fig. 13-1. Chemical structure of CS.

produce many semivolatile organic air contaminants[29]; therefore, such canisters must not be used in enclosed spaces for training. It is important for medical personnel to encourage commanders and trainers to deploy CS and other RCAs according to the most current training guidance.

The practice of heating CS capsules (national stock number 1365-00-690-8556) on an improvised aerosol generator (Figure 13-4) is currently the preferred method of CS dispersal inside a mask confidence chamber. The Uniformed Services University of the Health Sciences, Department of Preventive Medicine and Biometrics, Division of Environmental and Occupational Health is investigating this method of CS dispersal to determine the thermal degradation products produced.[39]

The metabolic effects and health issues associated with acute CS exposure and its hydrolysis products appear to have been thoroughly studied[26,40–48]; however, recent investigations into potentially harmful CS-derived compounds produced during thermal dispersion have raised new concerns. Many of these compounds have not been evaluated for their potential to produce acute or chronic effects,[28–31] and the current methods for analysis of CS and CS-derived compounds recommended by the National Institute for Occupational Safety and Health (NIOSH) are less than adequate given the current arsenal of instrumental and analytical techniques now available.

Fig. 13-2. Heat dispersion of CS canisters at Fort Meade, Maryland.
Photograph: Courtesy of TA Kluchinsky.

In 1961 Porter and associates[49] identified and quantified several compounds produced as a result of the thermal degradation of CS. They identified CS, CO, CO_2, Cl^-, NH_4, N_2O, C_2H_2, and water at temperatures ranging from 490°C to 625°C.[49] In 1969 McNamara et

Fig. 13-3. CS canisters being dispersed inside a room at Fort Meade, Maryland. This method is neither recommended nor permitted for mask confidence training; it is being performed here for research purposes only.
Photograph: Courtesy of TA Kluchinsky.

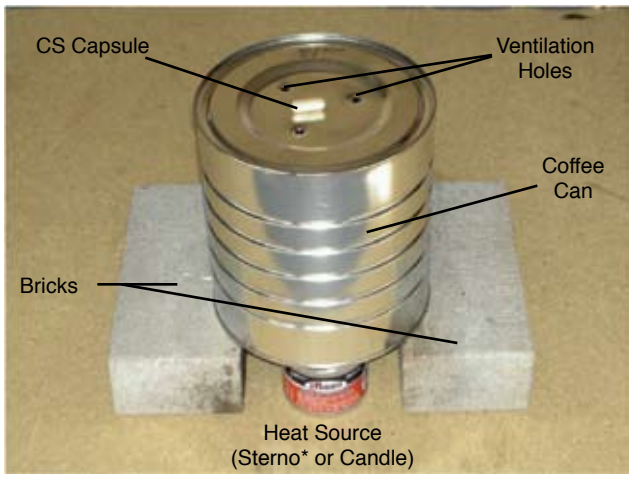

Fig. 13-4. Preferred method of heating CS capsules (national stock number 1365-00-690-8556) on an improvised aerosol generator.
Photograph: Courtesy of TA Kluchinsky and J Hout.
*Candle Corporation of America, Des Plaines, Il.

al[27] reported the pyrolytic decomposition products of CS as CS, CO, CO_2, H_2O, HCl, HCN, NH_3, N_2O_2 and C_2H_2. Further research by Kluchinsky et al[28–30] during 2000 and 2001 using heat-dispersed CS canisters (Figures 13-2 and 13-3) identified many additional thermal degradation products by trapping the contaminants on a polytetrafluoroethylene filter and analyzing them by open tubular gas chromatography coupled to mass spectrometry. Compounds observed in addition to CS and its isomer 4-chlorobenzylidenemalononitrile included 2-chlorobenzaldehyde, 2-chlorobenzonitrile, quinoline, 2-chlorobenzylcyanide, 1,2-dicyanobenzene, 3-(2-chlorophenyl)propynenitrile, *cis*- and *trans*-isomers of 2-chlorocinnamonitrile, 2,2-dicyano-3-(2-chlorophenyl)oxirane, 2-chlorodihydrocinnamonitrile, benzylidenemalononitrile, *cis*- and *trans*- isomers of 2-cyanocinnamonitrile, 2-chlorobenzylmalononitrile, 3-quinoline carbonitrile, and 3-isoquinoline carbonitrile.[28–30]

The CS-derived compounds observed were likely produced through rearrangements and by loss of cyano and chlorine substituents present on the parent CS compound. Especially noteworthy is the formation of 3-(2-chlorophenyl)propynenitrile, which is indicative of a loss of cyanide from the CS molecule. Although the metabolic effects of cyanide have been addressed in the open literature, the metabolic effects of *trans*- and *cis*-2-cyanocinnamonitrile, 3-quinoline carbonitrile, and 3-isoquinoline carbonitrile, which appear to be produced through free radical mechanisms, lack sufficient investigation.

Detailed sampling under similar conditions and analysis for inorganic salts (using the NIOSH methods 7904 and 6010 [modified] for HCN and 7903 for HCl) showed that HCN and HCl were present in air samples collected during high-temperature dispersion of CS.[28] The concentration of HCN identified during the dispersion of two CS canisters inside a 240 m^3 RCA training chamber (Figure 13-2 and 13-3) was found to be above the exposure level guidelines recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) and NIOSH.

The study group hypothesized that the formation of potentially harmful CS-derived compounds produced through free radical intermediates (*cis*- and *trans*- isomers of 2-cyanocinnamonitrile, 3-quinoline carbonitrile, and 3-isoquinoline carbonitrile), and the release of HCN, evidenced by the presence of 3-(2-chlorophenyl)propynenitrile, was temperature dependent. This hypothesis led to another study in which CS was heated in an inert atmosphere using a tube furnace.[30] Pure CS was used so that the effect of temperature on CS could be analyzed independently of the other compounds present in canisters, such as potassium chlorate, sugar, magnesium carbonate, and nitrocellulose. It was assumed that the tube furnace's effect on the production of CS-derived compounds could be generalized to that formed by high-temperature dispersion of CS canisters. By assuming that neat CS behaved in a similar manner as that found in canisters dispersing at an average temperature of 798°C (Figure 13-5), standardizing residence time in the tube furnace, and using an inert nitrogen carrier gas at a constant flow, it was shown that many of the organic degradation products observed earlier in a field environment were produced through heating. Additionally, the study identified tube-furnace–induced temperature ranges associated with the formation of the CS-derived compounds.

However, generalizing conclusions drawn from laboratory-based CS data to exposures from thermal dispersion of CS in a field environment must be done with caution. CS must be deployed appropriately during operations and training to ensure optimal safety. Use of CS capsules (Figure 13-4) is the only accepted method of CS dispersal for mask confidence training performed in an enclosed space (eg, tent, chamber, or building).

Clinical Effects

Acute Effects

CS is a peripheral sensory irritant that acts primarily upon the eyes, respiratory tract, and skin; acute exposure to CS presents itself very much the same as exposures to other RCAs.[50] Exposure almost instantly results in irritation, burning, and swelling of the conjunctivae of the eye, accompanied by excessive

Fig. 13-5. Insertion of a thermocouple into a hole drilled in a CS canister at Fort Meade, Maryland, to determine dispersal temperature.
Photograph: Courtesy of TA Kluchinsky.

tearing and uncontrollable closure of the eyelid. In some cases, the subject experiences an aversion to light. As the agent enters the respiratory tract, it causes irritation and burning in the nose and mouth as well as excessive nasal discharge and salivation. It causes pain and discomfort in the throat and chest, resulting in sometimes violent coughing spasms and difficulty breathing.[35] The respiratory effects are the most pronounced and most capable of causing individuals to flee from the exposure.[51] Irritation and reddening of exposed skin is quite common and is more pronounced with increased temperature, humidity, and concentration of the agent.[52]

Animal Studies

Acute oral toxicology studies. Acute oral studies involving CS in alcohol or water administered by esophageal catheter to rabbits and rats yielded median lethal doses (LD_{50}s) of 401 mg/kg and 822 mg/kg, respectively.[53] When CS was administered in polyethylene glycol to various animal species, the LD_{50}s were determined to be 231 mg/kg in male rabbits, 143 mg/kg in female rabbits, 1,366 mg/kg in male rats, 1,284 mg/kg in female rats, and 262 mg/kg in female guinea pigs.[40]

Acute eye toxicology studies. Solutions of up to 10 mg CS in methylene dichloride placed into the eyes of rabbits did not produce permanent ocular damage.[54,55] Immediate effects observed following administration were conjunctivitis that lasted for 30 to 60 minutes and erythema of the eyelid. CS administered into the eyes of rabbits via solutions of 0.5% to 10% CS caused conjunctivitis, chemosis, keratitis, and corneal vascularization, as well as denudation of the corneal epithelium and neutrophilic infiltration. When administered via thermal dispersion, the solid caused tearing at all doses, uncontrolled closure of the eyelids that increased with dose, and mild chemosis at the high doses that persisted for up to 3 days. The smoke also caused excessive tearing and swelling of the conjunctiva lasting 24 hours. All tissues were normal within 7 days.[54]

Acute skin toxicology studies. When 12.5 mg of CS in corn oil or acetone was applied to the dorsal skin of rabbits, guinea pigs, and mice, the effects were erythema and edema. These effects resolved within 7 days.[40]

Mutagenic potential studies. The mutagenic potential of CS and CS2 was investigated in microbial and mammalian bioassays.[56–59] The results were equivocal, but the Committee on Toxicology of the National Research Council reported in 1984 that, taken in their totality, the test of CS for gene mutation and chromosomal damage provides no clear evidence of mutagenicity.[60] Most of the evidence is consistent with nonmutagenicity, and in the committee's judgment, it is unlikely that CS poses a mutagenic hazard to humans.

Acute inhalation toxicology studies. Acute inhalation studies of CS were conducted in several animal species with CS generated as a smoke.[40,61] The acute inhalation (vapor exposure) median lethal doses (LCt_{50}s) are presented in Table 13-2. Studies by Weimar and associates[62] indicated that toxicity of CS varies depending upon the method of dispersion, arriving at the following order of toxicity: molten dispersion > dispersion in methylene dichloride > dispersion via thermal grenade.

Repeat exposures. Repeat exposures to thermally dispersed CS were conducted in rats and dogs for 25 days. The cumulative doses received were 91,000 $mg \cdot min/m^3$ and 17,000 $mg \cdot min/m^3$, respectively. No lethality occurred in the dogs, while 5 of the 30 rats exposed died, 2 at the cumulative dose of 25,000 $mg \cdot min/m^3$, and 3 at 68,000 $mg \cdot min/m^3$. No gross pathology was observed in the rats that died, nor in the six other rats sacrificed following the 25 days of exposure. During the exposure, the rats became hyperactive and aggressive, although no changes were found in the blood chemistry. The exposed rats lost almost 1% of their body weight, whereas the unexposed rats gained 20% during the 5-week period, although there was no difference in organ to body weight ratios. It was concluded from these studies that repeated exposures did not make the animals more sensitive to the lethal effects of CS. The animals that died during the exposures showed increased numbers of goblet cells in the respiratory and gastrointestinal tracts and conjunctiva, necrosis in the respiratory and gastrointestinal tracts, pulmonary edema, and occasional hemorrhage in the adrenals. The deaths appeared to be caused by poor transfer of

TABLE 13-2

ACUTE INHALATION TOXICITY OF CS IN ANIMALS

	LCt_{50} ($mg \cdot min/m^3$)	
Species	**CS Smoke**	**CS Aerosol**
Guinea pig	35,800	67,000
Rabbit	63,600	54,090
Rat	69,800	88,480
Mouse	70,000	50,110

LCt_{50}: the vapor or aerosol exposure that is lethal to 50% of the exposed population

oxygen from the lungs to the blood stream, probably because of edema and hemorrhage in the lungs and obstruction of the airways.[55] In other repeat exposures to neat CS aerosols in mice, rats, and guinea pigs for 120 days, it was concluded that concentrations below 30 mg/m^3 were without deleterious effects.[63]

Subchronic toxicology studies. Punte and associates[55] exposed 30 rats and 5 dogs to molten CS aerosol dispersed via an oil bath in a 200-L exposure chamber. Both species were exposed for 5 days per week; however, the time per day was varied. Dogs were exposed for 1 minute (680 mg•min/m^3) daily, resulting in a cumulative dose of 17,000 mg•min/m^3. Rats were exposed for 5 minutes (3,600 mg•min/m^3) daily, resulting in a cumulative dose of 91,000 mg•min/m^3. The only clinical presentation of CS exposure in the dogs was salivation, which resolved itself 1 minute postexposure. Six of the thirty rats died during the 5-week period; however, no gross pathological changes were found in these rats or the others sacrificed at the end of the study. Neither species exhibited significant differences from controls in body weight ratios of the heart, kidney, lungs, liver, or spleen.[55]

Chronic toxicology and carcinogenicity studies. CS has been referred to throughout the literature as an alkylating agent, and some alkylating agents are carcinogens. McNamara and associates[64] exposed groups of mice and rats to CS daily for 20 days. Representative groups were sacrificed at 6, 12, 18, and 24 months and examined for tumors. Examinations showed no significant increase in lung tumors between the exposed animals and controls. The data suggested that CS is not a potent carcinogen.[64]

A study by Marrs and associates[63] exposed mice to 55 60-minute exposures to aerosolized CS. At 1 year postexposure, the exposed mice did not experience a statistically significant number of deaths in comparison with the control group, and pathological examinations revealed no increase in tumors. Other than an increase in chronic laryngitis and tracheitis in the exposed group, there were no pathological differences between the two groups.[63]

CS2 was evaluated for carcinogenicity in the National Toxicology Program 2-year rodent bioassay. Compound-related nonneoplastic lesions of the respiratory tract were observed. The pathological changes observed in the rats included squamous metaplasia of the olfactory epithelium and hyperplasia and metaplasia of the respiratory epithelium. In mice, hyperplasia and squamous metaplasia of the respiratory epithelium was observed. Neoplastic effects were not observed in either rats or mice, and it was concluded that the findings suggest that CS2 is not carcinogenic to rats and mice.[65]

Human Studies

Respiratory effects. CS can enter the respiratory tract as a vapor, aerosol, or solid and take action on the nasopharyngeal, tracheobronchial, and pulmonary levels of the respiratory tract. In low concentrations, it irritates the pulmonary tract; at high concentrations, it can affect the respiratory system.[50] Gongwer and associates[66] exposed volunteers to various concentrations of CS through a facemask and by total body exposure to establish the concentration that would be intolerable. Following exposure, subjects were questioned and reexamined. The concentrations varied from 2 to 360 mg/m^3 and the time from 30 to 120 seconds. Upon exposure, subjects experienced irritation of the nose, throat, and chest. They also experienced coughing and had difficulty breathing; however, airway resistance was not significantly changed. These effects were resolved within minutes in fresh air. At levels of 10 to 20 mg/m^3, 50% of the study population found the concentration intolerable.[66]

In another study, Gutentag and associates[51] exposed trained and untrained volunteers to various concentrations of CS to determine the intolerable concentration. Subjects in a wind tunnel were exposed to concentrations varying from 5 to 442 mg/m^3 of CS generated by CS-acetone spray (3 μm), CS-methylene dichloride spray (1 μm), and an M18 grenade (0.5 μm). The respiratory system effects were the most pronounced and most capable of producing incapacitation. Exposure resulted in immediate burning of the nose, throat, and lungs that soon became painful. Tightening of the chest and difficulty breathing followed shortly. Airway resistance, however, remained unchanged. A portable breathing measuring device verified that subjects involuntarily gasped and held their breath upon exposure. All symptoms resolved after removal from the environment. Of the untrained study population, 50% found a concentration of 7 mg/m^3 intolerable.[51]

Other investigators exposed human volunteers to various concentrations, particle sizes, and durations of CS. Volunteers were able to tolerate the large particle size (60 μm) for 60 seconds, but those exposed to the small particle size (0.9 μm) could not.[67] When CS was dispersed in methylene dichloride (1.0 μm) and thermally (0.9 μm), the volunteers could tolerate 1.5 mg/m^3 exposures for 40 minutes. When the concentration was increased to 11 mg/m^3, the volunteers fled the chamber within 2 minutes.[52] Respiratory effects were similar to those noted by Gutentag in 1960 for all exposures.[51] Response times (defined as tolerance) did not vary depending upon the method of dispersion; however, the duration of tolerance was reduced with increased humidity, temperature, and exercise.[52]

McNamara and associates[27] summarized six experiments to determine the incapacitating concentration of CS. The experiments varied in concentrations (5–422 mg/m^3), method of dispersal, and exposure time (30–300 seconds). The incapacitating effects were the same at that noted by Gutentag and associates. The incapacitating concentration for 50% of the population was determined to be somewhere between 0.1 and 10 mg/m^3, depending upon the motivation of the exposed population. There was no difference in tolerance times among dispersal methods or for men over age 50. This study also concluded that incapacitation time was reduced with increased temperature and humidity.[27]

Beswick and associates[35] exposed 35 men to 1-μm particles of CS dispersed in a 100-m^3 chamber by the ignition of 1-g CS pellets. The concentration varied from 0.43 to 2.3 mg/m^3 over a period of 60 minutes. Symptoms of exposure included nasal pain and discharge, rhinorrhea, throat irritation, tightness and burning of the chest, and difficulty breathing. Subjects developed tolerance to the compound and were able to remain in the chamber for 60 minutes, despite the 4-fold increase in concentration. Postexposure measurements revealed no differences in peak flow, tidal volume, or vital capacities from those made before the exposure.[35]

Cole and associates[68] exposed several male volunteers to concentrations of 0.16 to 4.4 mg/m^3 in an exposure chamber. Ventilation minute volume was observed to decrease an average of 6% in the exposed population.[68]

Based upon the data presented, a variety of health-related values have been calculated. The NIOSH recommended exposure limit ceiling value is 0.4 mg/m^3. This ceiling value should not be exceeded at any time. The OSHA permissible exposure limit is 0.4 mg/m^3. This is the concentration of CS, averaged over an 8-hour workday, to which most workers can be exposed without adverse effect. The value considered immediately dangerous to life and health (IDLH) is 2 mg/m^3.[69]

In a final report to the deputy attorney general, Heinrich[70] stated that CS can be detected by the human nose at an odor threshold value of 0.004 mg/m^3. Blain[71] stated that concentrations of 0.004 mg/m^3 are detectable by the human eye and that concentrations of 0.023 mg/m^3 are detectable in the airways. He also stated that the ICt_{50}, or the concentration that is intolerable to 50% of the exposed population for 1 minute, is 3.6 mg/m^3. This value is consistent with the work of Punte, Gutentag, and McNamara.[72,73] A summary report produced by the Directorate of Medical Research at Edgewood Arsenal, Maryland, cites the LCt_{50} for molten CS as 52,000 mg•min/m^3 and 61,000 mg•min/m^3 by thermal grenade. The same report cites the ICt_{50} as ranging from 0.1 to 10 mg•min/m^3.[53]

Dermatological effects. CS exposure can result in a multitude of cutaneous reactions, such as allergic contact dermatitis, rashes, blisters, and burns. Exposure manifests itself as a delayed (several minutes) stinging sensation that is less remarkable than the reaction of the eyes and nose. The severity of the reaction depends upon several variables including (but not limited to) the method of dispersal, CS concentration, temperature, and humidity.[72]

Gutentag and associates[51] conducted a series of patch tests on several volunteers, using CS protected from the air, CS in a porous gauze covering, a 10% CS solution in methylene dichloride, and a 20% CS solution in methylene dichloride. The porous gauze covering produced the greatest skin effect, causing four of four volunteers to develop vesicles surrounded by erythema. The 10% CS solution caused no skin reaction in three of three volunteers. The researchers also exposed subjects to wind-dispersed CS via CS-acetone spray (3 μm), CS-methylene dichloride spray (1 μm), and an M18 grenade (0.5 μm). Subjects reported burning on exposed areas of the skin that increased with the presence of moisture. The burning sensation lasted for several hours and recurred when the affected area was moistened. Heavy exposures produced vesiculation and reddening that resembled a second-degree burn.[51]

Hellreich and associates[74] exposed the arms of volunteers to an average concentration of 300 mg/m^3 for 15 to 60 minutes via thermal grenade. Within 5 minutes of exposure, subjects experienced a burning sensation of the skin; concentration multiplied by time (Ct) exposures of 4,440 and 9,480 mg•min/m^3 produced immediate reddening of the skin. Upon removal from the exposure area, subjects washed their arms and found the burning sensation to increase. Within 30 minutes of removal from the environment, all symptoms of exposure resolved.[74] In a follow-on study, Hellreich and associates[75] used patches to test the dermal effects of CS on the arms of volunteers at four temperature conditions. The patches were taken off at specified exposure times to give exposures at 37°C with 98% relative humidity (RH), 14°C with 41% RH, 20°C with 95% RH, and 22°C with 72% RH. Higher temperatures and humidity resulted in a lower Ct required to produce skin effects.[75]

Rengstorff[76] documented CS exposures in firefighters in Washington, DC, during the 1968 riots, when law enforcement agents used CS to disperse rioters from buildings. Some structures were set ablaze during the rioting; as firemen entered the building, the heat, movement, and force of the water from their hoses

caused the CS to reaerosolize. This caused swelling and reddening of the exposed skin in many firemen.[76]

Weigand and associates[72] documented a case in which soldiers experienced first- and second-degree burns from exposure to CS1 during a training exercise. Upon exposure, all soldiers experience a stinging sensation on their exposed skin. At 2 hours postexposure, some soldiers cleaned their body of the agent and changed their contaminated clothing; however, many did not. Those who did not bathe or change clothes developed severe erythema and blistering of the skin 14 to 16 hours postexposure.[72]

Weimar and associates[77] conducted patch testing on four volunteers with a 1% CS trioctylphosphate solution and solutions of 0.01% to 1.0% on the forearms of five volunteers. One subject experienced a stinging sensation for the first 30 minutes of the patch test. When the CS volume was increased from 0.01 to 0.025 mL on both bare skin and patch test skin, no reactions were noted. The researchers also applied patches of CS trioctylphosphate solutions ranging from 0.1% to 1% CS to the foreheads of five volunteers, which created stinging at all concentrations. Increasing the temperature from 75°C to 105°C and duplicating the tests produced similar results.[77]

Ballantyne and associates[78] exposed the skin of 52 volunteers to concentrations of CS ranging from 0.001% to 0.005% in glyceryl triacetate by saturating their clothes and bare skin with the solutions. The skin effects presented as sunburn-like irritation that started around the eyes and spread across the body, with hands and feet being affected last. The scalp and ears were not usually affected. The symptoms diminished after 10 minutes, even with the presence of soaked clothing. Erythema was observed hours later; however, no vesication, edema, or desquamation occurred. Minor cuts and abrasions were not affected differently than healthy skin.[78]

Ophthalmologic effects. CS causes instant irritation, burning, and swelling of the conjunctivae of the eye. It is most often accompanied by lacrimation and blepharospasm and in some cases, photophobia.[54] Several studies, animal and human, have been conducted to evaluate the ophthalmologic effects of this agent.[51,52,76,78–80] An early study exposed military and civilian volunteers in a wind tunnel to CS dispersed via CS-acetone spray (3 μm), CS-methylene dichloride spray (1 μm), and an M18 grenade (0.5 μm). Eyes of the subjects were instantly affected by burning that lasted 2 to 5 minutes, followed by conjunctivitis that remained up to 30 minutes. Tearing was produced almost immediately and persisted up to 15 minutes, whereas reddening of the eyelids persisted for an hour. Uncontrollable blinking sometimes accompanied the exposure. Some subjects complained of eye fatigue lasting 24 hours postexposure. For nearly 1 hour postexposure, 5% to 10% of the subjects experienced photophobia.[51]

Punte et al[52] evaluated the effect of CS particle size on the human eye by exposing six volunteers in a wind tunnel to CS particles of small size (0.9 μm mass median diameter) disseminated from a 2% CS solution in methylene dichloride and large-size (60 μm mass median diameter) particles from a powder hopper. Only the eyes were exposed. Two of five men exposed to small particles were able to tolerate exposure for 60 seconds, while all six men exposed to large particles were able to tolerate the exposure. Postexposure, all subjects had difficulty seeing. Recovery was 90 seconds for the smaller particles and 280 seconds for the larger particles. The study concluded that small particles produce eye irritation much faster than large particles; however, larger particles prolong the eye effect.[52]

Rengstorff[76] tested the ocular effects of CS on human volunteers by exposing them to concentrations of 0.1 to 6.7 $mg \cdot min/m^3$ of CS (thermally dispersed) or CS2 (powder dispersed) for 20 seconds to 10 minutes. Subjects who kept their eyes open could read a vision chart and showed no significant change in visual acuity caused by the exposure.[76] In a follow-on study, the researchers administered 0.1% or 0.25% CS solutions in water and 1% solution in trioctylphosphate directly into the eyes of several volunteers. In addition to those symptoms experienced by Gutentag's study group, the subjects were unable to open their eyes for 10 to 135 seconds postexposure. Examination revealed no corneal damage.[79,80]

Ballantyne and associates[78] evaluated the ocular effects of CS by drenching clothed military volunteers with solutions containing 0.001% CS (3 men, 2 women), 0.002% CS (3 men, 2 women), 0.003% CS (2 men, 2 women), and 0.005% CS (22 men, 11 women) in glyceryl triacetate. Subjects were either drenched individually or as a group. For individual drenching, subjects were saturated at the head, trunk, and leg level at a rate of 15 L over a 15-second period. Subjects were observed and questioned at 20 minutes postexposure. For group drenching, the spray was directed at the group for a period of 1 minute. The group exercised before and after the drenching. Individuals were questioned during the exercises and as a group after showering. CS was found to affect the eye within seconds, causing stinging, uncontrollable blinking, and tearing. The irritant did not blur vision; rather, blurred vision was caused by tears. Symptoms resolved in 3 to 5 minutes.[78]

Gray and Murray[81] and Yih[82] reported an increase in eye injury caused by the use of CS sprays in

Great Britain during the 1990s. Ocular injuries were caused by the discharge of the agent at close range, which infiltrated the conjunctiva, cornea, and sclera with CS powder. This exposure sometimes resulted in complications such as symblepharon, pseudopterygium, infective keratitis, trophic keratopathy, posterior synechia, secondary glaucoma, cataracts, hyphema, vitreous hemorrhage, and traumatic optic neuropathy.[81–83]

Gastrointestinal effects. A review of the literature revealed no human studies assessing oral toxicity of CS; however, incidents of intentional and accidental ingestion of this compound have been documented. Most cases involved children who accidentally ingested CS they found while playing in impact areas of military installations. An intentional ingestion occurred during an attempted suicide by a healthy young man. For treatment, he was given large amounts of saline cathartics, and, after abdominal cramps and diarrhea, he fully recovered. An accidental ingestion occurred when a male swallowed a 820-mg CS pellet thinking it was a vitamin. He was treated with liquid antacid and viscous lidocaine and administered droperidol intravenously. After vomiting twice and having six watery bowel movements, he recovered fully.[3]

Solomon et al[84] documented an incident in which seven people accidentally consumed CS-contaminated juice in central Israel. Five of the seven presented to a primary care clinic within minutes with complaints of eye irritation, tearing, headache, facial irritation, and burning of the mouth and throat. The other two people presented the next day with complaints of nausea, abdominal pain, and diarrhea. When inspecting the juice container, investigators found several small CS pellets partially dissolved at the bottom. Upon questioning, patients revealed that the burning sensation did not occur immediately upon consumption; rather, it presented minutes later.[84] This presentation of symptoms is consistent with research by Kemp and Willder, who found that subjects who consumed sugar contaminated with CS did not feel symptoms for 30 seconds after consumption. This delayed onset of symptoms was attributed to the masking of the CS by the sweetness of the sugar.[85] The two patients who presented with symptoms the following day did not experience any bad flavor. All patients were observed for 24 hours and released. The amount of ingestion was estimated to be less than 25 mg; the lethal amount for a 70-kg man is about 14 g. The author concluded that it might be impossible for a person to accidentally consume a lethal amount because of the low taste threshold and local irritation caused by the compound.[84]

Long-term effects and severe medical complications. Although studies show that the effects of CS are short-lived and typically resolve within minutes of exiting the contaminated area, three cases of prolonged airway dysfunction following exposure to the agent have been reported. Studies show that exposure to high levels of respiratory irritants is associated with the development of reactive airways disease syndrome (RADS) in some individuals.[86] Hu et al[87] was the first to make the association between CS and RADS in his assessment of the use of CS in South Korea, after noting that the community displayed the typical symptoms of RADS (prolonged cough and shortness of breath) after heavy exposure to CS.[87] Roth and Franzblau[88] later reported a previously healthy 53-year-old man who, after exposure to a CS/OC mixture, experienced a decreased exercise tolerance, chronic cough, fatigue, and irregular pulmonary function tests that persisted for months postexposure.[88] Hill et al[89] reported a 31-year-old prison worker who was occupationally exposed to CS during a "shake-down." In the months following exposure, the subject continued to suffer from symptoms consistent with RADS.[89] The Himsworth report on British law enforcement use of CS concluded that exposure to the agent could result in death by inflicting pulmonary damage leading to pulmonary edema; however, the authors noted that the concentration required to cause this complication is several hundred times greater than the exposure dosage that produces intolerable symptoms.[37,38] No deaths attributed to CS exposure have been documented.[72]

CS is also a powerful skin sensitizer that can cause allergic contact dermatitis with rashes or hypersensitivity upon repeated exposure to the agent.[50] A 1960 report[90] of CS exposures in plant workers by Bowers and associates revealed three general reactions to exposure: a single local reaction with no recurrence upon repeated exposure, local responses with progressively shorter latent periods, and generalized-type eruptions with progressively shorter latent periods. The author suggests that anyone who experiences one of these reactions should not return to CS-contaminated atmospheres.[90]

OC (OLEORESIN CAPSICUM)

OC is a naturally occurring mixture of compounds extracted from more than 20 different species of the capsicum plant, which include chili peppers, red peppers, jalapeno, and paprika (eg, *Capsicum frutescens, Capsicum annuum*). More than 100 different compounds have been identified in various OC extracts. The composition of the extract, and hence its precise physiological and toxicological properties, can vary depending on

numerous factors, including the type and age of plant used for isolation and the method of extraction. Many of the physiological responses induced by OC are due to a family of compounds known as capsaicinoids. OC is 0.1% to 1.0% capsaicinoids by dry mass. The main capsaicinoid of interest as an irritant and RCA is capsaicin (*trans*-8-methyl-*N*-vanillyl-6-noneamide). The capsaicinoids content of OC is approximately 70% capsaicin, 20% dihydrocapsaicin, 7% norhydrocapsaicin, 1% homocapsaicin, and 1% homodihydrocapsaicin.

Historically, capsicum was used as a weapon by the ancient Chinese and Japanese police. In 1492 native Mexicans burned pepper in oil to create an irritating and suffocating smoke.[91] OC in small doses is used medicinally as a topical analgesic or counter-irritant. Capsaicin spray is also used in the pharmaceutical industry to induce cough for testing antitussive candidates.[92] Recently PAVA (nonivamide), a structural analog of capsaicin, was synthesized. PAVA, which can be used instead of naturally derived OC sprays, is believed to have similar but safer effects and more consistent ingredients than the natural form of OC.[4,93]

Physical Characteristics and Deployment

Capsaicin (Chemical Abstracts Service [CAS] registry number 404-86-4) has a molecular weight of 305.41 and a molecular formula of $C_{18}H_{27}NO_3$ (See Figure 13-6; Table 13-1). An odorless crystalline to waxy compound, capsaicin has limited solubility in water. OC is a derivative of hot cayenne peppers. PAVA (CAS 2444-46-4) has a molecular formula of $C_{17}H_{27}NO_3$ (Figure 13-7) and a molecular weight of 293.4.[93,94]

Because of its highly effective irritant properties, OC has found widespread use in various military, government, and civilian agencies for riot control and individual protection. OC is also available to the general public for personal protection. US forces deployed to Somalia carried nonlethal packages that included OC. Military police from several US Army divisions as well as several Marine Corps units, who have used OC in the past, are currently investigating its capabilities and supporting its use.[10,95] Numerous formulations of OC have been developed and marketed (commonly referred to as pepper spray, pepper mace, and pepper gas), but there appears to be no standardization.

Major factors separating one OC spray from another are the delivery device, carrier, and propellant system.[95] Currently, the most popular carrier is isopropyl alcohol. Additional carriers have included Freon, Dymel-22 (both made by DuPont, Wilmington, Del), and methylene chloride. However, with the exception of isopropyl alcohol, most OC carriers and propellants are currently banned or have use restricted by the 1987 Montreal Protocol, which attempts to regulate the use of chemicals with the potential to adversely affect the ozone layer.

The use of isopropyl alcohol as a carrier complicates the toxic effect of OC in two ways. First, isopropyl alcohol and other volatile carriers readily evaporate in the environment, and evaporation rates from OC fog and OC mist are greater than from OC streams, making it challenging to calculate the actual concentration of OC (ie, dose) on the target tissue. Second, isopropyl alcohol has physiological effects (as do the other over 100 constituents of oleoresin), causing a mild transitory injury (grade 4 on a scale of 10) when applied to rabbit eyes.[96] Additionally, the interaction of the other capsaicinoids in the oleoresin with capsaicin have not been well defined.

A variety of dissemination devices for OC exist, including many commercial preparations, and the method of choice depends largely on the number of expected subjects. These devices range from small items such as fake pens and pressurized cans, used to incapacitate subjects at close range, to grenades and cartridges for shotgun-mounted launchers, used to control groups of individuals from a distance. Some dissemination devices release OC as a fine mist or fog; others spray a stream of OC towards the subject. More recently OC has been dispensed in a "pepper ball"—a gel ball (similar to a recreational paint gun ball), fired from a high pressure air gun, that hits the individual and breaks on contact, releasing aerosolized dry OC.[97]

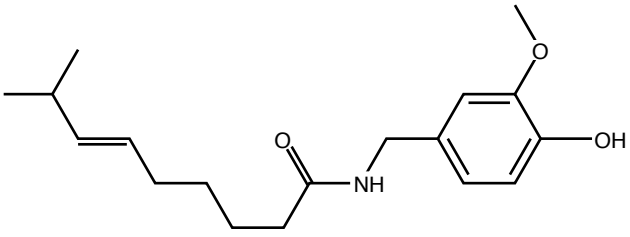

Fig. 13-6. Chemical structure of capsaicin.

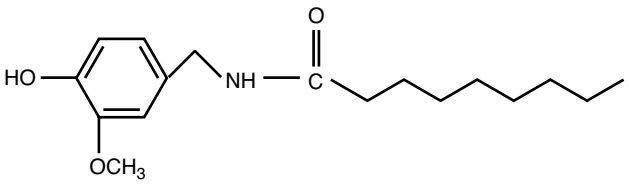

Fig. 13-7. Chemical structure of pelargonyl vanillylamide.

Physiological Effects

Capsaicin is a member of the vanilloid family of chemical compounds and binds to the vallinoid receptor subtype 1 (VR1) on sensory neurons; the VR1 receptor was discovered in 1997 using capsaicin as the ligand.[98] VR1, now known as TRPV1, is a member of the transient receptor potential (TRP) superfamily of receptors. TRPV1 is activated, in part, by excessive heat (>43°C) or abrasion, which explains why a major sensation following exposure to peppers is burning and heat. Mice deficient in TPRV1 receptors are defective in nociceptive, inflammatory, and hypothermic responses.[99] Thus, capsaicin does not cause a chemical burn, only the sensation of one. TRPV1 is also involved in purinergic signaling by the bladder urothelium, and its activation leads to a bladder distension sensation.[100]

Many of the acute respiratory effects induced by capsaicin in laboratory animals and humans are associated with the release of bioactive compounds such as substance P, neurokinin A, and calcitonin gene-related peptide from sensory nerves innervating these tissues.[4,73] The actions of these compounds result in clinical symptoms associated with exposure to capsaicin: bronchoconstriction, mucous secretion, edema of the tracheobronchial mucosa, enhanced vascular permeability, and neutrophil chemotaxis.

Clinical Effects

OC, CS, and CN are considered peripheral sensory irritants that interact with sensory nerve receptors in the skin or mucosae to produce local sensation (discomfort, itching, burning sensation, or pain) together with related local and some systemic (autonomic) reflexes. The effects subside after removal of the stimulus and do not result in any long-term adverse sequelae. The principle effects of these agents are on the eye, respiratory tract, and skin. On the eyes, depending on the concentration, the effects are local itching, discomfort, or pain with excessive lacrimation and blepharospasm as local reflexes.[2]

Pain stimuli can be suppressed through a variety of mechanisms (eg, medication and alcohol, ignored through discipline, or overcome by anger and aggression). The sensory irritation induced by OC can involve inflammation and swelling in respiratory tissues and the eyes. The ocular swelling forces the eye to involuntarily shut, which cannot be overcome or suppressed[95] (people who are described as "unaffected" by OC spray still display involuntary eye closure and temporary blindness[101]).

Acute Effects

As with any compound, the physiological and toxicological effects following acute exposure to OC are a function of the dose and route of exposure. In humans, these can range from mild irritant effects that quickly resolve following removal of the stimulant to lethality, which can occur within 1 hour of exposure. The most immediate affect following exposure to OC in a spray is in the eyes, with lacrimation and blepharospasm. Following inhalation, OC can also induce changes in the respiratory system, including nasal irritation, severe coughing, sneezing, and shortness of breath. A burning sensation in the skin is another common effect. Finally, neuromotor dysfunction and accompanying loss of motor control can result. High doses of capsaicin can induce serious and sometimes lethal toxicity on the respiratory, cardiovascular, and sensory nervous system.

The LD_{50}s for capsaicin are 0.56 mg/kg (intravenous), 7.6 mg/kg (intraperitoneal), 7.8 mg/kg (intramuscular), 9.0 mg/kg (subcutaneous), 190 mg/kg (oral), 512 mg/kg (dermal), and 1.6 mg/kg (intratracheal).[102] The most probable cause of death is respiratory paralysis. The estimated oral lethal dose in humans ranges from 0.5 to 5.0 g/kg.[102]

Respiratory Effects

The respiratory system is a major target following exposure to OC owing to the highly sensitive TRPV1 receptors located in the mucosa of the respiratory tract. These effects have been characterized in several reviews.[73,95] The initial symptoms of exposure are often a tingling sensation accompanied by the protective mechanisms of coughing and decreased inhalation rates. Thereafter, depending on dose, intense irritation accompanied by severe pain occurs. Profound vasodilatation and secretion occur in the nasal passages, both of which are considered protective mechanisms. In lower portions of the respiratory tract, capsaicin induces bronchoconstriction, pulmonary edema, and in severe cases of poisoning, apnea and respiratory arrest.

Dermatological Effects

Although OC is most effective on the eyes and mucous membranes, it does irritate the skin, which contributes to the overall unpleasant effects of the compound.[73] Following contact with skin, OC can induce intense burning pain, tingling, edema, erythema, and occasional blistering, depending on dose. The sensations usually last less than an hour following

exposure. In humans, repeated applications of OC to facial skin produced initial symptoms of irritation, but the intensity and duration of the effect decreases to the point of no observable reaction.[103] Repeated short-term exposure, in a matter of minutes, can also lead to an exaggerated response to concomitant pathologies, such as experimental inflammation and allergic dermatitis.

Ophthalmologic Effects

OC is a potent ocular irritant. The clinical signs of exposure to pepper spray include lacrimation, inflammation of the conjunctiva, redness, burning, pain, swelling, and blepharospasm. As mentioned previously, victims will involuntarily shut their eyes to the inflammatory effects of OC. Although the individual may voluntarily hold their eyes shut for up to 30 minutes following exposure, visual acuity normally returns within 2 to 5 minutes following decontamination.[12] When directly applied to the eye, OC can cause neurogenic inflammation, unresponsiveness to chemical and mechanical stimuli, and loss of the blink reflex, which can last for days following exposure.[73]

Gastrointestinal Disturbances

The effects of OC on the gastrointestinal tract and its impact on nutrition have been investigated by several researchers and were recently summarized by Olajos and Salem.[73] Many of the studies have focused on direct toxicity of intestinal epithelial cells following administration of capsaicinoids and the association between toxicity and altered fat uptake. A study of the effect of intragastric capsaicin on gastric ulcer using a rat model found that 2 to 6 mL/kg aggravated existing gastric mucosal damage.[104]

Other Physiological Responses

In addition to the well-described effects of OC on the eyes and respiratory system, capsaicin has a direct effect on the thermoregulatory system. Capsaicin has a long history of use in the laboratory for studying the physiological processes of temperature regulation.

Long-Term Effects and Severe Medical Complications

When mice were fed ground *Capsicum annuum* (high dose = 0.5%-10% body weight) for a 4-week period, slight glycogen depletion and anisocytosis of hepatocytes were noted with the high-dose group, but it was concluded that *C annum* was relatively nontoxic to mice.[105] Likewise, rats fed capsaicin (50 mg/kg per day) or capsicum (500 mg/kg per day) for a period of 60 days had significant reductions of plasma urea nitrogen, glucose, phospholipids, triglycerides, total cholesterol, free fatty acids, glutamic pyruvic transaminase, and alkaline phosphatase, but these effects were considered mild.[106] Thus, although repeated doses of capsaicin are associated with some biochemical alterations, it appears to be well tolerated in experimental animals at high doses.

OTHER RIOT CONTROL COMPOUNDS

PS (Chloropicrin)

PS (CAS 76-06-2, also called nitrochloroform) was used as a tear gas (harassing agent) during World War I. Beginning in the early 1920s, PS was used commercially as an antitheft device and, since the 1950s, as a soil fumigant to kill root-destroying fungi, nematodes, and soil insects that damage delicate plants and vegetables, such as strawberries. It is currently a restricted-use pesticide in the United States but has wider use in other countries.[107] Although used as a harassing agent, PS acts much like a pulmonary agent and is often classified as such. As a security device, safes and vaults were frequently outfitted with chemical vials that released PS when breeched. Several companies produced these devices between 1920 and 1950. The number and location of PS-laden safes sold or still in circulation is unknown, and modern-day accidental exposures sporadically occur. As recently as 2003, in Beloit, Wisconsin, a safe owner was exposed to approximately 112 g of PS after the storage vial accidentally cracked; and in 1999 a pregnant worker in an Iowa bank was accidentally exposed to PS from a shattered vial.[108] Both victims sustained eye and skin irritation, with the latter victim also reporting irritation in the throat. The 2004 incident in Sofia was the most recent newsworthy deployment of PS. It was originally believed that a disgruntled individual threw a bomb containing PS into the crowded area, but Bulgarian authorities later reported that the incident occurred by accident when a 50-year-old man dropped a vial of PS from his pocket.[17,18]

The United States produces approximately 10 million pounds of PS per year for use as a soil fumigant, either by itself or, owing to its odor, as a warning agent for other odorless fumigants such as methyl bromide.[109–111] Human exposures resulting from envi-

ronmental application of PS as a fumigant have been reported. Most recently, 165 persons reported symptoms consistent with PS exposure following application of 100% PS at a concentration of 36 kg per acre to 34 acres in Kern, California.[112,113] Although PS dissipates readily in the environment, trace amounts are found in drinking water disinfected by chlorination.[60,114,115] Despite its historical and current uses, PS-induced toxicity resulting from inhalation, ingestion, or direct skin or eye contact remains poorly documented.

Physical Characteristics and Deployment

The molecular weight of PS is 164.4, and its molecular formula is CCl_3NO_2 **(**Figure 13-8). PS is an oily, volatile, colorless to faint-yellow liquid with an intensely irritating odor. Weaponized PS is primarily disseminated through wind dispersion, the simplest technique of delivering an agent to its target. It consists of placing the agent directly on or adjacent to the target immediately before dissemination (eg, antitheft devices placed on safes). Analogous dispersion methods were used in the early 20th century for delivery of chlorine, phosgene, and mustard gases. It was learned from the 2003 Kern, California, incident that when PS was injected 17 to 18 inches into the soil, people residing one quarter of a mile downwind experienced irritating effects.[112] See Table 13-3 for a summary of the characteristics of DM and other agents.

Physiological Effects

The immediate physiological effect of PS is sensory irritation via stimulation of the trigeminal nerve endings located in the nasal mucosa, which leads to the clinical signs of exposure: a burning sensation of the nasal passages, inhibition of respiration, and lacrimation.[111,116] As an irritant, PS causes cellular lesions at the site of exposure (ie, lung lesions following inhalation, dermal lesions following contact with skin, and forestomach lesions following ingestion). Although these clinical and pathological effects have been characterized, the mechanisms of toxicity, particularly the biotransformation of the parent compound and the toxicity of the metabolites, are poorly understood.[117] It has been known for some time that PS can react directly with hemoglobin to form methemoglobin and that the toxicity of PS in mice is linked to the oxidative state of hemoglobin.[117,118] However, the contribution of these laboratory observations to the tissue damage observed in the clinic has yet to be resolved.

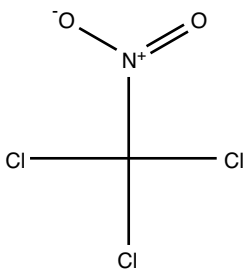

Fig. 13-8. Chemical structure of PS.

Other studies conducted in the 1940s suggested that the lacrimatory effect may be due, in part, to a selective reaction of PS with certain tissue dehydrogenases (eg, pyruvate dehydrogenase and succinate dehydrogenase).[119] Likewise, a causal relationship between these metabolic effects and toxicity has not been established. Rapid reductive dechlorination of PS to $CHCl_2NO_2$ by glutathione and other tissue thiols in vitro suggests that metabolites may be mediators of toxicity, but major differences in urinary metabolites of the compounds only partially support this hypothesis.[117] More recent evidence suggests a novel metabolic pathway for PS that involves conversion to raphanusamic acid; this study suggested that toxicity was mediated by the parent compound rather than metabolites.[117]

Clinical Effects

The major organs affected following acute exposure to PS are the eyes, skin, and respiratory tract.[69] With increasing doses or prolonged exposure times, systemic toxicity and lethality are observed. The dose of PS required to induce acute symptoms appears to be intermediate between the corresponding doses of chlorine and phosgene. Unlike with phosgene, there is no latent period between PS exposure and clinical symptoms.[60] "Chloropicrin syndrome" is characterized by unusual taste; eye tearing; nose and throat irritation; neurological symptoms (headache, nausea, and vomiting); shortness of breath; and anxiety.[111] The IDLH for PS is 2 ppm (1 ppm=6.72 mg/m^3) and the estimated LCt_{50} is 2,000 mg•min/m^3.[96] The inhalation LD_{50} in cats and pigs appears to be 800 mg/m^3 for a 20-minute exposure.[120] Acute pulmonary edema and dyspnea were observed in both species, and emphysema was reported in the pig. In mice, the LD_{50} is reported at 66 mg/m^3 for a 4-hour exposure.[120] The murine intraperitoneal LD_{50} for PS is 15 mg/kg, and the rat oral LD_{50} is 250 mg/kg.[117,121]

Respiratory effects. Inhalation of a sensory irritant causes inhibition of respiration and Kratschmer reflex. In the laboratory, inhibition of respiration is often measured by the dose required to cause a 50% decrease in

respiration (RD_{50}).[122] PS exposure in mice at the RD_{50} dose (8 ppm) for 5 days, 6 hours per day, results in nasal lesions of the respiratory epithelium consisting of moderate exfoliation, erosion, ulceration, and necrosis coupled with minor squamous metaplasia and inflammation.[116] Moderate ulceration and necrosis of the olfactory epithelium, coupled with serous exudates and moderate lung pathology, were also observed. Collectively, the PS pathology was similar to that observed following an RD_{50} exposure to chlorine and displayed a distinct anterior–posterior severity gradient. The significant toxicity in the posterior nasal cavity following inhalation of PS or chlorine was likely the result of the agents' low water solubilities, which prevented significant absorption in the anterior nasal cavity.

The human toxicity of PS following inhalation is primarily restricted to the small to medium bronchi, and death may result from pulmonary edema, bronchopneumonia, or bronchiolitis obliterans.[123] As little as 1.3 ppm may cause respiratory irritation in humans.[109] The NIOSH, OSHA, and ACGIH exposure limit for PS is 0.1 ppm (time-weighted average of 0.7 mg/m^3).[69] The NIOSH IDLH level of 2.0 ppm is based partly on studies conducted in the early 1930s that determined that a few-second exposure to 4 ppm renders a man unfit for action.[69,112,124] Symptoms in humans resulting from environmental or occupational exposures to PS include pain (burning) and tightness in the chest, shortness of breath, sore throat, dyspnea, irritation, asthma exacerbation, and cough.[111,112,125] The lowest published toxic concentration in humans is 2 mg/m^3 (unknown exposure time), which produced lacrimation and conjunctiva irritation, and the lowest reported human lethal dose is 2,000 mg/m^3 for a 10-minute exposure.[69]

Dermatological effects. Direct exposure of skin to PS leads to irritation, itching, rash, and blisters.[108,111,112] The minimal dose required to cause these effects is unknown.

Ophthalmologic effects. PS causes eye irritation beginning at 0.3 to 0.4 ppm, which appears to be below the threshold of odor (approximately 1 ppm).[109,124,126] Clinical symptoms of PS-induced ocular irritation include immediate lacrimation, pain, and burning. In 1995 three dockworkers were exposed to PS that had leaked from a shipping container.[111] All three victims complained of burning and stinging in the eyes. Additionally, in the 2003 Kern, California, exposures, of the 165 persons complaining of PS-induced reactions, 99% (164) of them reported eye irritation (82% reported lacrimation, and 54% reported pain or burning of the eyes).[112]

Gastrointestinal disturbances. Following ingestion of PS, a corrosive effect on the forestomach tissue is the principal lesion.[114] Rats exposed to PS (10–80 mg/kg) for 10 days demonstrated corrosion of the forestomach with histopathological findings including inflammation, necrosis, acantholysis, hyperkeratosis, and epithelial hyperplasia. In humans, acute exposure to PS in the atmosphere from environmental sources and occupational accidents has been associated with an unusual taste, stomach and abdominal cramping, abdominal tenderness, diarrhea, vomiting, nausea, difficulty swallowing, and in rare cases, bloody stools.[111,112]

Other physiological responses. Additional clinical and toxicological observations associated with acute PS exposure in humans include neurological manifestations (headache, dizziness, and fatigue); cyanosis; general neuromuscular tenderness; peripheral numbness; painful urination; chest wall pain; elevations in creatine phosphokinase; and low-grade rhabdomyolysis.[111,112]

Long-term effects and severe medical complications. Long-term or repeated exposures to PS are associated with damage to the kidneys and heart, and may result in hypersensitivity to subsequent PS exposures. No adequate data is available to assess the mutagenic, carcinogenic, teratogenic, or reproductive toxicity of PS in humans.[60]

CN (1-Chloroacetophenone)

CN is also known as Mace from its chemical name, **m**ethyl chloro**ace**tephenone. The first chemical Mace product is widely regarded as the original tear gas.[127,128] Although it is the trademarked name for CN, the term "mace" is commonly used generically to refer to any RCA. After the United States entered the First World War, American and British chemists investigated CN and found it to be one of the most effective lacrimators known. Its lacrimatory effects and persistence were equal to or slightly greater than bromobenzyl cyanide, and its chlorine was less expensive than bromine. CN is very stable under normal conditions and does not corrode steel. It is a crystalline solid that can be dissolved in a solvent or delivered in thermal grenades.

Physical Characteristics and Deployment

CN (CAS 532-27-4, also known as *w*-chloroacetophenone, *a*-chloroacetophenone, phenacyl chloride, 2-chloro-1-phenylethanone, and phenyl chloromethyl ketone) is a gray solid with an apple blossom odor. It has a molar mass of 154.5, corresponding to a molecular formula of C_8H_7ClO (Figure 13-9). Its molar solubility at 20ºC is 4.4×10^{-3} mol/L (68 mg/100 mL) in water. Hydrolysis of CN is very slow in water even when alkali is added.[71] Melting and boiling points are 54ºC

TABLE 13-3

CHARACTERISTICS OF PS, CN, DM, AND CR

Properties	PS	CN	DM	CR
Molecular formula	CCl_3NO_2	C_8H_7ClO	$C_{12}H_9AsCIN$	$C_{13}H_9NO$
Former/ Current use	RCA and war gas/ Preplant soil fumigant	War gas/RCA	War gas, vomiting agent/obsolete RCA	RCA/RCA
Physical state*	Colorless oily liquid	Colorless to gray crystalline solid	Light yellow to canary green crystals	Pale yellow crystalline solid
Odor	Strong, sharp, pungent and highly irritating odor	Fragrant (like apple blossoms)	Odorless or not pronounced. May be mildly irritating	Pepper-like
Freezing and/ or melting point	Melting point: -64°C Freezing point: -69°C	Melting point: 57°C	Melting point: 195°C with slight decomposition	Melting point: 72°C
Vapor pressure	20 mm Hg at 20°C	0.0041–0.005 mm Hg at 0°C	Negligible at ambient temperature. 4.5×10^{-11} mm Hg at 25°C	Data not available
Density:				
Vapor (relative to air)	5.6 times heavier	5.3 times heavier		
Liquid	1.66 g/mL	1.187 g/mL at approximately 58°C		
Solid		1.318 g /cm^3 at approximately 20°C	Bulk: < 1g/cm^3 Crystal: 1.65 g/cm^3 at 20°C	
Solubility:				
In water	Insoluble	Relatively insoluble; slow hydrolysis; 1.64 g/100 mL at 25°C	0.044 g/L at 37°C, very slow hydrolysis	Relatively insoluble and not hydrolyzed
In other solvents	Soluble in organic solvents, lipids	Soluble in carbon disulfide, ether, and benzene	Slightly soluble in benzene, xylene acetone, alcohols. Acidic solutions prevent hydrolysis	Is sometimes suspended in solutions of propylene glycol, but data on solvents not available
Hydrolysis products	Carbon dioxide, bicarbonate, chloride, nitrate, and nitrite. May also produce toxic vapors such as oxides of nitrogen, phosgene, nitrosyl chloride, and chlorine	HCl	Diphenylaminearsenious oxide and HCl	Data not available
Decontamination:				
Clothing	Move to fresh air; remove clothing, do not wear again until properly laundered or discard	Move to fresh air; remove clothing and wash before wearing again	Move to fresh air; remove clothing and wash before wearing again	Move to fresh air; remove clothing and wash before wearing again

(**Table 13-3** *continues*)

Table 13-3 *continued*

Skin	Copious soap and water	Copious soap and water	Copious soap and water	Copious soap and water or use 5% or 10% sodium bicarbonate solution, which is more effective than water
Equipment	Copious soap and water	Copious soap and water	Copious soap and water	Copious soap and water
Persistency:				
In soil	Half life from 8 hours to 4.5 days	Short	Persistent	Persistent
On material	Half-life is 20 days or less in sunlight	Short	Persistent	Persistent
Skin and eye effects	Irritation, itching, rash, and blisters on exposed skin. Eye lacrimation, pain, and burning appear below the threshold of the odor. Very potent lacrimator	Primarily skin erythema that is bradykinin-mediated and acute. Can develop blisters and burns on moist tissue due to HCl formation. Strong lacrimator with conjunctivitis, eye pain, and blepharospasm. High dose can produce chemical injury to the eyes	Significant nasal discharge. The amount needed to cause skin irritation and erythema is above that needed for irritation of respiratory and gastrointestinal tract. Repeated dose leads to sensitization. Only slight eye irritation reported when throat and chest irritation are present	Burning of skin, particularly in a hot and moist environment. Erythema and blistering are possible with lengthy exposure. Produces violent lacrimation in the eyes, with burning, conjunctivitis, and lid erythema
Respiratory effects	Immediate burning sensation in nasal passages, choking, and inhibition of respiration. Can cause lung lesions	Upper respiratory irritation, cough, dyspnea. Can also produce tissue burns of the airway and pulmonary lesions if dose is significant	Sneezing, coughing,. salivation, and congestion of the nose and upper airway to produce a feeling of suffocation	Burning sensation and pain in the upper respiratory tract with subsequent feeling of suffocation
Other effects			Produces initial nausea followed by violent retching and vomiting, which can occur 20–30 minutes after initial exposure. Can also produce perspiration, chills, mental depression, abdominal cramps, and diarrhea lasting several hours	Anxiety, fatigue

*At standard temperature and pressure.

Data sources: (1) Sidell F. Riot control agents. In: Sidell F, Takafuji E, Franz D, eds. *Medical Aspects of Chemical and Biological Warfare.* In: Zajtchuk R, Bellamy RF, eds. *Textbook of Military Medicine.* Washington, DC: Department of the Army, Office of The Surgeon General, Borden Institute; 1997: Chap 12. (2) US Department of the Army. *Potential Military Chemical/Biological Agents and Compounds, Multiservice Tactics, Techniques, and Procedures*. Washington, DC: DA; January 10, 2005. FM 3-11.9. (3) Somani SM, Romano JA Jr, eds. *Chemical Warfare Agents: Toxicity at Low Levels*. Boca Raton, Fla: CRC Press; 2001. (4) US Army Center for Health Promotion and Preventive Medicine. Detailed facts about tear Agent chloropicrin (PS). USCHPPM Web site. Available at: http://chppm-www.apgea.army.mil/dts/docs/detps.pdf. Accessed December 27, 2006. (5) Chloropicarin as a Soil Fumigant. US Department of Agriculture, Agricultural Research Service Web site. Available at: http://www.ars.usda.gov. Accessed November 2, 2005. (6) Centers for Disease Control and Prevention. Exposure to tear gas from a theft-deterrent device on a safe—Wisconsin, December 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:176–177.

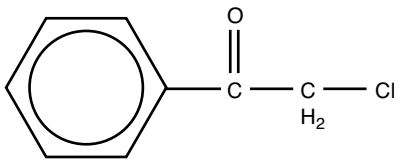

Fig. 13-9. Chemical structure of CN.

and 247°C, respectively. Density of the solid is 1.318 g/cm^3 at 20°C, and density of the liquid is 1.187 g/m^3 at 58°C. The vapor is 5.3 times heavier than air.[14]

Although CN was not produced in sufficient quantities to be used in World War I, Japan used the agent as early as 1930 against aboriginal Taiwanese.[128] CN was used as the tear gas of choice for the 3 decades after its introduction, but its use markedly declined after the development of CS.[96]

Physiological Effects

CN and CS are SN2 alkylating agents with activated halogen groups that react with nucleophilic sites and combine with intracellular sulfhydryl groups on enzymes such as lactic dehydrogenase to inactivate the enzymes. The effects are transient because the enzymes are rapidly reactivated. It has been suggested that tissue injury may be related to inactivation of certain of these enzyme systems. Pain can occur without tissue injury and may be mediated by bradykinin. On contact with skin and mucous membranes, CN releases chlorine atoms, which are reduced to hydrochloric acid, causing local irritation and burns.[129]

CN, which is converted to an electrophilic metabolite, reacts with sulfhydryl groups and other nucleophilic sites of biomolecules. Alkylation of sulfhydryl-containing enzymes leads to enzyme inhibition with disruption of cellular processes. Castro[130] investigated the effects of CN on human plasma cholinesterase, based on the potential to disrupt enzyme functions. He found CN to inhibit the cholinesterase via a nonsulfhydryl interaction, concluding that the toxic effects of CN may be due to alkylation of sulfhydryl-containing enzymes.[130]

Animal Studies

Toxicology. Comparative acute and repeat dose toxicity studies have been conducted in various animal species (review and summarized by McNamara et al[27]). The studies produced highly variable results, prompting subsequent studies in the mid-1960s designed to provide more quantitative data. In these studies, CN in acetone was dispersed from commercially available thermal grenades. Sublethal effects observed on exposure to CN consisted of lacrimation, conjunctivitis, copious nasal secretions, salivation, hyperactivity, dyspnea, and lethargy, which occurred in all animals. CN is considered a more toxic lacrimator than CS or CR, and at high concentrations it has caused corneal epithelial damage and chemosis. CN, as well as CS and CR, causes almost instant pain in the eyes, excessive flow of tears, and closure of the eyelids.[71]

The primary cause of death following CN inhalation appeared to be from pulmonary damage. The LCt_{50} values for various species were reported to be 8,878; 7,984; and 7,033 mg•min/m^3 for the rat, guinea pig, and dog, respectively. The pathological observations in the animals that died from CN inhalation included pulmonary congestion, edema, emphysema, tracheitis, bronchitis, and bronchopneumonia. The pathological findings in animals following death by CN inhalation reported by Ballantyne and Swanston[40] included congestion of alveolar capillaries, alveolar hemorrhage, and excessive secretions in the bronchi and bronchioles. The researchers also reported areas of acute inflammatory cell infiltration of the trachea, bronchi, and bronchioles. McNamara et al[131] exposed guinea pigs, dogs, and monkeys to thermally generated CN on 10 consecutive days at C*t*s ranging from 2,300 to 4,000 mg•min/m^3, for a total of 31,445 mg•min/m^3.[131] This dosage would be expected to be lethal to about 75% of the guinea pigs and 100% of the monkeys if administered as a single dose. However, these exposures resulted in the death of only five guinea pigs and no deaths in the monkeys. When administered in divided dosages, the toxicity of CN is considerably lower. These findings were confirmed in additional studies in which dogs were exposed on 10 consecutive days to C*t*s ranging from 3,000 to 7,000 mg•min/m^3 for a total dosage of 60,000 mg•min/m^3. Subsequent repeated dose studies in guinea pigs, dogs, and monkeys exposed daily for 10 days to C*t*s ranging from 4,200 to 13,000 mg•min/m^3 were lethal to the majority of the animals for all species tested. Overall, these studies demonstrated the lack of cumulative toxicity of CN when administered in divided dosages.

Kumar et al[132] subjected mice to multiple exposures of CN and CR at concentrations equivalent to 0.05 LCt_{50}—87 mg/m^3 for CN and 1,008 mg/m^3 for CR—for 15 minutes per day for 5 and 10 days. Biochemical endpoints measured included blood glucose, plasma urea, transaminase enzymes (serum glutamic:oxaloacetic transaminase and serum glutamic:pyruvic transaminase), liver acid phosphatase, liver glutathione levels, and hepatic lipid peroxidation (malondialdehyde formation). Clinical parameters affected by repeated exposures included decreased hepatic glutathione

and increased lipid peroxidation. Hepatic acid phosphatase increased after the 5-day CN exposure, and the glutathione levels decreased after the 10-day CN exposure. CN-induced elevation in acid phosphatase levels reflected the release of lysosomal enzyme from the liver, which is indicative of tissue injury. CR exposure did not produce any significant alteration of the biochemical parameters. Additionally, hyperglycemia was observed after exposure to CN, an effect previously reported by Husain et al.[133] It was suggested that the hyperglycemia was induced by the stress-mediated release of epinephrine, which is known to elevate glucose levels. Significant decreases in body weight gain were also noted on exposure to these compounds, with CN having a more prominent effect on body weight.

The acute mammalian inhalation toxicity of CN was 3 to 10 times greater than CS toxicity in rats, rabbits, guinea pigs, and mice. Lung pathology in the CN-exposed animals was also severe, consisting of patchy acute inflammatory cell infiltration of the trachea and bronchioles, as well as of more edema and more evidence of early bronchopneumonia than with CS.[134]

Ocular effects. In a variety of studies, mice and rats exposed to CN aerosols for 13 weeks had no findings of gross clinical signs except for irritation of the eyes, including opacity. No microscopic lesions were noted compared to controls. Avoidance and the intense lacrimation and blepharospasm are indicative of defensive mechanisms caused by CN ocular irritation. High concentrations of CN may result in chemical injury to the eyes, with corneal and conjunctival edema and erosion, or ulceration, chemosis, and focal hemorrhage.[135–137] CN-induced ocular effects on the rabbit eye have been investigated by Ballantyne et al[138] and Gaskins et al.[139] The effects included lacrimation, chemosis, iritis, blepharitis, and keratitis, and the severity was dependent on the formulation.

Sublethal effects observed on exposure to CN consisted of lacrimation, conjunctivitis, copious nasal secretions, salivation, hyperactivity, dyspnea, and lethargy, which occurred in all animals. At high concentrations CN has caused corneal epithelial damage and chemosis. Like CS and CR, CN causes almost instant pain in the eyes along with excessive flow of tears and closure of the eyelids.[71] The ocular effect of conjunctivitis and dermal erythema persisted for 3 to 7 days postexposure in animal studies.[71] Lacrimation persisted for about 20 minutes postexposure; conjunctivitis and blepharospasm persisted for up to 24 hours.[27]

Cutaneous effects. Exposure to CN has been associated with primary irritation and allergic contact dermatitis.[140–142] CN is a potent skin irritant and is more likely to cause serious injury to the skin than CS. Exposure to high doses of CN results in skin injury that may consist of severe generalized itching, diffuse and intense erythema, severe edema, and vesication. CN is also considered to be a more potent skin sensitizer than CS.[140]

Carcinogenicity testing. The National Institutes of Health conducted a carcinogenicity bioassay in rats and mice with CN, finding no indication of carcinogenetic activity of CN in male rats exposed by inhalation. The evidence was equivocal in female rats based on the findings of an increase in mammary gland fibroadenomas. The 2-year inhalation study in both male and female mice did not suggest any carcinogenic activity.[143]

Human Studies and Effects

The effects caused by CN in humans are similar to those of CS, but more severe. The harassing dose and toxicity of CN are also greater than for CS. The effects of exposure to low concentrations usually disappear within 20 to 30 minutes. Based on animal toxicology of CN, the initial LCt_{50} estimated for humans was 7,000 $mg \cdot min/m^3$, which was subsequently revised and established as 14,000 $mg \cdot min/m^3$. Persistence of these effects (rhinorrhea, lacrimation, blurred vision, conjunctivitis, and burning of the throat) was negligible, with no clinical signs and symptoms noted approximately 10 minutes following cessation of exposure. Values for the ICt_{50} of CN range from 25 to 50 $mg \cdot min/m^3$. These ICt_{50} values are comparable to those of DM. The estimated LCt_{50} for CN dispersed from solvent in grenades is 7,000 $mg \cdot min/m^3$, although some researchers have reported estimates between 8,500 and 25,000 $mg \cdot min/m^3$.[144]

Volunteer acute exposure studies. In human volunteer studies, the immediate effects of exposure to CN were a burning sensation or stinging in the eyes, nose, throat, and exposed skin, followed by lacrimation, salivation, rhinorrhea, and dyspnea. Common signs observed were rhinorrhea, lacrimation, and conjunctivitis, and reported symptoms included blurred vision, burning of the throat, and some less frequent but more severe symptoms of difficulty in breathing, nausea, and burning in the chest.[55] Punte et al[55] studied the effects of CN on human subjects exposed to aerosols at C*t*s below 350 $mg \cdot min/m^3$. This dosage is considered the maximum safe inhaled aerosol dosage for humans. Punte et al[55] also studied CN dispersed from solvent in grenades and found the maximum safe inhaled dose to be 500 $mg \cdot min/m^3$. Other estimates range from 8,500 to 25,000 $mg \cdot min/m^3$.

Respiratory effects. Exposed individuals may experience lacrimation, conjunctivitis, conjunctival edema,

upper respiratory irritation, cough, dyspnea, and skin burns, as well as pulmonary lesions if exposures occur in confined spaces.[144] Hospitalizations were reported by Thorburn following the release of CN into 44 prison cells.[144] Twenty-eight inmates sought medical attention, and eight of them were hospitalized. All eight complained of malaise, lethargy, and anorexia. Five had pharyngitis, three of whom developed pseudomembranous exudates several days later. Three also developed tracheobronchitis with purulent sputum, but no infiltrates were seen on chest radiographs. Four inmates had facial burns, and three had bullae on the legs. The most severely affected had first- and second-degree burns over 25% of his body. Another inmate was admitted 5 days after the incident with a papulovesicular rash on his face, scalp, and trunk, which had appeared 2 days earlier. Ten inmates were treated as outpatients for first- and second-degree burns, and six had localized papulovesicular rashes. Ten had conjunctivitis with edema of the conjunctiva, and in some, the eyelids were closed by the swelling. None had corneal injuries or permanent eye damage. The patients with laryngotracheobronchitis were treated with bronchodilators, postural drainage, and positive-pressure exercises. Two were given short-term, high doses of steroids, but none received antibiotics. One required bronchodilator therapy 3 months later, but the others made prompt recoveries.

Stein and Kirwin[145] reported another prison incident in which inmates confined to individual cells were exposed to a "prolonged gassing" with CN estimated to last 110 minutes. The windows and doors were closed and the ventilation was off. The CN was disseminated by at least six thermal grenades of CN, fourteen 100-g projectiles of CN, and more than 500 mL of an 8% solution of CN. The calculated dosage of the exposure from just the CN projectiles was a Ct of 41,000 $mg \cdot min/m^3$. Following the exposure some of the prisoners had coughing and varying degrees of illness, and at least three received medical treatment, although details were not available to the authors. One prisoner was found dead under his bunk 46 hours postexposure. Other prisoners reported that the prisoner who died had "red eyes," vomited bloody material, and had sought medical attention on several occasions. The autopsy findings included cyanosis of the face and head, edema and congestion of the lungs, alveolar hemorrhage, necrosis of the mucosal lining of the lungs, bronchopneumonia, and no evidence of physical injury. The lungs had subpleural petechiae, hyperemia, mild edema, and patchy areas of consolidation. Microscopic examination showed bronchopneumonia clustered around exudate-filled bronchioles. The larynx and tracheobronchial tree were lined with an exudative pseudomembrane, which on microscopic examination proved to be a fibrin-rich exudate containing polymorphonuclear leukocytes and their degenerating forms. There was no evidence of gastrointestinal hemorrhage, but other organs had passive hyperemia.[145]

Chapman and White[146] reported the death of an individual who had locked himself in a room in his house during an altercation with the police. A single CN grenade containing 128 g of CN was thrown into the room, which was approximately 27 m^3. The individual remained in the room for 30 minutes, for a Ct of 142,000 $mg \cdot min/m^3$. This exposure is about 10 times higher than the estimated human LCt_{50}. On admission to the hospital, his respirations were 24 per minute, conjunctiva were suffused, pupils were small and unreactive, and mucoid discharge from his nose and mouth was abundant. His lungs were clear, and an occasional premature ventricular contraction was evident on the electrocardiogram. He remained in a semicomatose condition for approximately 12 hours, then suddenly developed pulmonary edema and died. The relevant findings on autopsy included cyanosis, frothy fluid in the mouth and nose, acute necrosis of the mucosa of the respiratory tract with pseudomembrane formation, desquamation of the lining of the bronchioles with edema and inflammation of the walls, and a protein-rich fluid in most of the alveolar spaces. Foci of early bronchopneumonia were also present.

Stein and Kirwan[145] also obtained information on three other cases of death following CN exposures from other medical examiners. Although details were scanty, the autopsy findings were similar in all three cases. The individuals were all confined individually in relatively small spaces, and the exposures were for 10 minutes in one case and for hours in the other two.[145]

Thus deaths from high concentrations of CN may occur and have been reported. Postmortem examinations revealed edema and congestion of the lungs, alveolar hemorrhage, necrosis of the mucosal lining of the lungs, and bronchopneumonia.[144–146]

Cutaneous effects. Although in animal studies the cutaneous effects seen consisted mainly of erythema, in humans, pain can occur without tissue injury and may be bradykinin mediated. Local tissue irritation and burns may result from the hydrochloric acid formed on moist tissues.[60]

In his 1925 textbook, Vedder stated that in field concentrations, CN does not damage human skin, although the powder might produce burning or slight rubefaction and sometimes small vesicles.[147] In 1933 Kibler[148] reported a case of primary irritant dermatitis in a soldier and three cases in civilian employees who probably had allergic dermatitis from working around

CN for years. In 1941 Queen and Stander[149] reported the case of a 43-year-old military recruit who spent 5 minutes exposed to an atmosphere of CN while masked. After removing the mask and leaving the chamber he developed a severe allergic reaction. Within 5 minutes of exiting the chamber, he complained of generalized itching, which progressively worsened until by 4 hours he had developed a diffuse and intense erythema over his entire body, except for his feet and the part of his face that was covered by the mask. His temperature was 38.9°C (102°F), which rose to 39.4°C (103°F) by the next day. By 48 hours postexposure, vesication and severe subcutaneous edema had strikingly altered his facial appearance. This was accompanied by severe generalized itching. These signs subsided over the next 4 days, and the desquamation which was profuse at day 6 gradually decreased. This recruit had been exposed to a similar CN exercise 17 years previously and developed itching, but had not been exposed in the interim.[149]

Another case of cutaneous hypersensitivity was reported by Madden in 1951,[150] in which a police officer received an initial exposure to CN, and 5 years later on repeated exposure developed recurrent attacks of what was probably allergic contact dermatitis. The source of the repeated exposures was unrecognized until the police officer realized that he was using outdated CN bombs for eradication of rodents on his property. He developed a severe dermatitis on his legs with each use over a period of 5 years. When a small area of one leg was intentionally exposed to CN, an acute contact dermatitis appeared and subsided within 8 hours. [150]

Holland and White[141] studied the skin reactions in humans following CN application. Irritation began within 10 minutes and became more severe when the agent was left in place. By 60 minutes, 0.5 mg CN had produced irritation and erythema on the skin of all the people tested. These effects disappeared when the CN was removed, but recurred transiently when the areas were washed during the subsequent 12 hours. In all cases, diffuse redness appeared in an area up to three times the original contact area. At doses of over 2 mg, localized edema occurred but subsided after 24 hours. When applied dry in doses of 0.5 to 2 mg, the redness disappeared within 72 hours. At higher doses and at all doses applied moist, the redness became raised and papular. The papules coalesced to form a ring of vesicles at about 48 hours. Two weeks later, the lesions were evident as faint areas of hyperpigmentation. These effects contrasted to those of CS also evaluated in these studies. CS at doses under 20 mg caused no irritation or erythema, and no vesiculation resulted from CS at doses of 30 mg or less. Thus CN is a more potent primary irritant on the skin than CS.

Ophthalmologic effects. The irritation caused by CN in the eye signals avoidance and, by causing lacrimation and blepharospasm, initiates a defense mechanism.[3] High levels of CN can produce chemical injury to the eyes characterized as corneal and conjunctival edema, chemosis, and loss of corneal epithelium.[136] Physical injuries may also occur following dispersion via grenade-type tear gas devices.[135,136] More lasting or permanent effects may occur when CN is released at close range (within a few meters), particularly if the dose is from a forceful blast from a cartridge, bomb, pistol, or spray.

Using records from the files of the Armed Forces Institute of Pathology in Washington, DC, Levine and Stahl[151] reviewed eye injuries caused by tear gas weapons. Although many of the histories were incomplete, in about half of the cases the injuries were self inflicted or accidental. In the other cases, the injuries were caused by a second person firing a weapon at close range with intent to injure the patient. In some instances, particles of agglomerated agent were driven into the eye tissues by the force of the blast, and a possible chemical reaction caused damage over months or years. In other instances, the injury was probably caused by the blast or other foreign particles rather than by CN. The authors carefully pointed out that features of the weapon, such as the blast force, the propellant charge, the wadding, and the age of the cartridge (in older cartridges, the powder agglomerates and forms larger particles) should be considered in evaluating eye damage from CN.[151]

Rengstorff[152] also concluded that traumatic effects of blast are a considerable factor that must be considered when determining the cause of permanent eye injury in CN exposures. Although permanent eye damage has been reported from the use of CN weapons at close range, separating the effects of the weapon from those of the compound is difficult. There is no evidence that CN at harassing or normal field concentrations causes permanent damage to the eye.[3]

Other physiological responses. The 1984 National Research Council study[60] reported histopathological changes following CN exposures including hemorrhage, perivascular edema, congestion of the alveolar capillaries, occluded bronchioles, and alveolitis. Renal histopathology demonstrated congestion and coagulative necrosis in the cortical renal tubules in CN exposed mice. Hepatic histopathology consisted of cloudy swelling and lobular and centrolobular necrosis of hepatocytes.[60]

Long-term effects and severe medical complications. Between 1958 and 1972, 99 human subjects underwent experimental exposures to CN at Edgewood Arsenal. Of these, 69 were exposed by aerosol

and 30 by direct application to the skin. However, exposure data is available on only 68 subjects. The aerosol exposures ranged from 0.15 to 3.63 minutes with C*t* dosages between 6 and 315 mg•min/m^3, and the cutaneous doses ranged from 0.01 to 0.025 mL, applied to bare or clothed arms. Effects on the aerosol-exposed subjects were transient, generally resolving within minutes of removal of the CN. Experienced subjects appeared to be tolerant, and closing their eyes often increased tolerance. Predominant effects were ocular and included lacrimation, blepharospasm, conjunctivitis, and, rarely, palpebral edema. Respiratory effects were nasopharyngeal irritation, rhinorrhea, and, rarely, dyspnea. Skin irritation was prominent on shaved areas. Other rare effects were headache and dizziness. Of the dermally exposed subjects, only one had erythema at the exposure site, which lasted 7 hours. Five had normal laboratory results, which included urinalyses, complete blood count, blood urea nitrogen, alkaline phosphatase, and serum glutamic oxalotransferases 7 days postexposure. Among the 68 subjects with exposure records, there were probably no permanent ocular or pulmonary injuries. These short, low-level exposures caused transient effects on the eyes and respiratory system, and recovery was complete within minutes. Minimal information is available on the dermal effects, but sensitization is considered likely, causing allergic contact dermatitis and possible systemic allergic reactions such as pulmonary fibrosis on reexposure, although there is no evidence that this occurred among the Edgewood subjects.[60]

DM (Diphenylaminearsine)

DM (CAS 578-94-9, also known as diphenylaminoarsine and 10-chloro-5,10-dihydrophenarsazine) is one of three arsenical war gases developed near the conclusion of World War I.[153] The other two closely related chemicals, DA (diphenylchloroarsine) and DC (diphenylcyanoarsine), proved to have much less military importance. German scientists first discovered DA in 1913 (German patent application 281049), but producing the compound proved difficult and expensive. In 1918 Major Robert Adams, working at the University of Illinois, discovered a simpler and more economical way to produce DM (which then took on the common name adamsite).[154] The United States produced DM by the end of the war but did not use it; however, very incomplete reports suggest that Italy may have used it.[155] In World War II all belligerent states produced DM, and smoke generators containing DM were developed.

After the war it was recognized that DM had applications as a possible RCA because of its harassing characteristics; it was eventually classified by the military as a vomiting agent and a sternutator. For riot control purposes, because of its minimal effects on the eye, DM was mixed with the tearing agent CN, and this preparation was used by US troops during Vietnam.[156,157] Today DM is considered obsolete as an RCA and has no other application.[73] Current US research on DM focuses on the environmental impact of the parent compound and its breakdown products near former production, storage, and disposal sites.[158,159]

Physical Characteristics and Deployment

The molecular weight of DM is 277.59, and its molecular formula is $C_{12}H_9AsClN$ (Figure 13-10). DM is a yellow-green (depending on purity), odorless (or possessing a faint bitter almond smell) crystalline substance with low volatility. It is practically insoluble in water and slightly soluble in organics such as benzene, xylene, toluene, and alcohols.[153] DM can be disseminated as a dry powder by thermal or explosive methods or by spraying the molten materials or solutions of the material.[27,153] The M6A1 (a basic Army riot control munition) and commercial grenades (such as the Spede-Heat [Defense Technology, Casper, Wyo]) are methods used to deploy DM.[153,160] Laboratory methods of dispersion include molten DM and acetone dispersions.

Physiological Effects

Only a few reports deal with the biological conversion of organoarsenical compounds. Even less data exists on the metabolism of DM. However, one recent report suggests the arsenic atom As(III) of DM is oxidized by manganese peroxide into As(V), which results in the release of chloride and the incorporation of dioxygen.[158] The relationship between this metabolism and the acute toxicity of DM in humans is unknown.

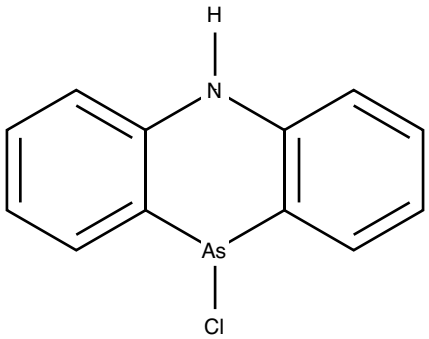

Fig. 13-10. Chemical structure of DM.

Clinical Effects

Acute effects. The acute effects in laboratory animals and human volunteers following inhalation of DM are strikingly variable.[27,161] Numerous factors can contribute to variability in laboratory studies (eg, differences in agent preparation, delivery method, dose, endpoint of interest). Clinical observations following exposure to DM have been reported as immediate or delayed; the delay in onset of pulmonary and systemic effects following DM exposure was considered advantageous because the delay meant that significant exposure could occur before the individual was warned to don a protective mask.[27,153,160]

In laboratory animals, clinical signs of toxicity immediately following exposure to high doses of DM have been studied in several species.[27] Immediately following exposure, the clinical signs of toxicity in mice (LCt_{50}: 46,245 mg•min/m^3); rats (LCt_{50}: 12,710–66,856 mg•min/m^3, depending on method of dispersion); and pigs (LCt_{50}: 6,599–29,888 mg•min/m^3, depending on the method of dispersion) included transient hyperactivity and followed within a few minutes by lacrimation and salivation. Lethargy and labored breathing were observed within 5 to 15 minutes and persisted for 1 to 2 hours.

In dogs (LCt_{50}: 13,945–28,428 mg•min/m^3, depending on the method of dispersion), immediate clinical signs of toxicity included extreme restlessness (jumping and barking) accompanied by salivation, retching, vomiting, and ataxia. Postexposure dogs also became hypoactive, with gagging and vomiting occurring periodically for 24 hours and lasting for about 1 week. Following lethal doses, most deaths in dogs occurred within the first week.

During exposure, clinical signs of toxicity in monkeys (LCt_{50}: 13,866–22,814 mg•min/m^3, depending on the method of dispersion) included salivation, vomiting, rhinorrhea, ataxia, and difficulty breathing. Postexposure monkeys exhibited wheezing, ptosis, and lethargy. Coughing and vomiting persisted for 24 to 48 hours, and depressed breathing preceded death.

During exposure to a toxic dose of DM, goats (LCt_{50}: 8,076–12,072 mg•min/m^3, depending on the method of dispersion) displayed hyperactivity, shaking of the head, rearing on hind legs, licking, chewing, frothing at the mouth, ataxia, convulsions, and bloating. Clinical signs postexposure included hypoactivity, kneeling, gagging, and vomiting. All goats were bloated upon death.

Lastly, in swine (LCt_{50}: 35,888–56,361 mg•min/m^3, depending on the method of dispersion), salivation, frothing at the mouth, ataxia, and irregular breathing were observed during exposure. During the first 2 weeks postexposure, pigs had difficulty breathing, lost weight, and appeared emaciated.

The acute lethal inhalation dose of pure DM in humans is not known but was estimated by the Chemical Research and Development Laboratories, Edgewood Arsenal, in 1959.[153] This risk assessment was based largely on lethality data collected in mice, pigs, and dogs from studies that used highly purified DM. These data were combined to produce a composite lethality dose–response curve for mammals, which was thought to capture the dose-lethality relationship in humans. From this curve, an LCt_{50} value of 14,000 mg•min/m^3 was established. Based on subsequent studies conducted between 1959 and 1965, which further characterized the lethal dose in seven species of laboratory animals and addressed different methods of dispersion, the predicted human LCt_{50} following exposure to highly purified DM was reduced to 11,000 mg•min/m^3. Given the variability in the dose–response curves in laboratory animal studies depending on the method of exposure or dissemination (as outlined above) and purity of the agent, the predicted human LCt_{50} was determined to be 44,000 mg•min/m^3 and 35,000 mg•min/m^3 for DM dispersed from the M6A1 and commercial thermal grenades, respectively.

Inhalation of DM has been linked to at least one human fatality.[153] In this incident, 22 sleeping males were exposed to the agent via a DM generator for 5 or 30 minutes at an estimated concentration of 1,130 to 2,260 mg/m^3. In the single fatality, postmortem examination revealed emphysema of the subcuataneous tissues of the neck, mediastinum, plura, and pericardium. Emphysematous bullae were scattered over the lungs, which were springy and had a bluish discoloration. Histological examination revealed pathology in the entire respiratory tract, edema and congestion of the epiglottis, superficial ulceration and acute diffuse inflammation of the trachea and bronchi, pseudomembrane formation in the trachea and bronchi, lung congestion, edema, hemorrhage, and bronchopneumonia.

The immediate incapacitating effects (irritation effects, local effects) and the delayed incapacitating effects (systemic effects) of DM in humans have been examined using volunteers. The incapacitating dose of DM following a 1-minute exposure ranged from 22 to 220 mg/m^3 (22–220 mg•min/m^3).[153] The concentration range spans an order of magnitude because intolerability is defined as the desire to leave a contaminated area, which is due, in part, to the population's degree of motivation to resist. Other researchers suggest that the effective immediate incapacitating dose of DM is as low as 0.14 mg/m^3 for a 1-minute exposure.[162] The clinical signs of immediate irritation included a burn-

ing sensation and pain in the eyes, nose, throat, and respiratory tract; uncontrollable cough; violent and persistent sneezing; lacrimation; and copious flow of saliva. In addition to irritant effects on tissues at the site of exposure, DM also has systemic incapacitating effects (ie, nausea and vomiting), which persist following termination of exposure. Based on studies using human volunteers, the inhalational ICt_{50} for systemic effects was determined to be 370 mg•min/m^3.

Postmortem observations in laboratory animals that received a lethal dose of DM have been reported in five species, and the primary cause of death for all species was lung damage.[153] In monkeys, pneumonitis; ulcerative bronchiolitis; and tracheitis, edema, and congestion of the lungs were reported. Bronchiolitis and tracheitis was also observed in guinea pigs. Dogs demonstrated hyperemia of the larynx and trachea, with signs of edema, congestion of the lung, and bronchopneumonia. In mice and rats, atelectasis, emphysema, reticular cell proliferation, respiratory epithelial proliferation, and interstitial leucocytic infiltration of the bile duct were observed. DM has also been shown to alter blood chemistry in laboratory animals.[153] Changes include alterations in leukocytes, serum enzymes, hematocrit, and prothrombin time.

Respiratory effects. In the respiratory passages and lungs, DM causes sneezing, coughing, salivation, congestion of the nose and walls of the pharynx, and a feeling of suffocation.[27,55] Viscous nasal discharge, characterized as a yellowish-orange material in monkeys, has been reported in laboratory animals and human volunteers.[156,160] A World Health Organization report characterized the clinical symptoms in the respiratory tract following DM exposure as initial tickling sensations in the nose, followed by sneezing and mucous discharge. The irritation spreads into the throat, followed by coughing and choking, with eventual affects observed in the lower air passages and lungs.[162]

Dermatological effects. Direct application of high doses of DM, 10 to 100 mg suspended in corn oil, onto rabbit skin resulted in necrosis and erythema, but neither effect was reported at a 1-mg dose.[27] Although these results identify DM as a potential skin hazard, several controlled exposures to DM aerosols in human volunteers and laboratory animals suggest that the dose required to cause acute skin irritation is well above that known to induce irritation and toxicity in other tissues.[55,153] One study in monkeys did report facial erythema following a moderate dose of aerosolized DM, but the pathology was likely the result of the animals rubbing their faces because of significant nasal discharge.[160] Repeated exposure to DM may lead to sensitization in susceptible persons.[153] Elevated environmental temperature, high relative humidity, and friction of the agent with the skin may be contributory factors to skin damage.

Ophthalmologic effects. Depending on the dose and method of administration, irritation of the eye is observed following exposure to DM, but ocular irritation is often not considered the main immediate effect at low doses.[163] For example, human volunteers exposed to airborne concentrations of DM up to 100 mg•min/m^3 (a dose causing nose, throat, and chest irritation) reported no initial eye irritation.[55] Other reports using human volunteers reported slight irritation of the eyes and lacrimation at doses causing nose and throat irritation and initial weak immediate ocular irritation.[157,162] In rabbits, a suspension of DM in corn oil was administered intraocularly to six groups of animals (0.1–5.0 mg/eye) and observed for 8 to 14 days.[27] The low dose (0.1 mg/eye) was determined to be the "no observable adverse effect" level; whereas transient conjunctivitis was observed following administration of 0.2 mg per eye; transient conjunctivitis and blepharitis were observed with the 0.5 mg per eye dose; and the high doses, 1.0 and 5.0 mg per eye, caused corneal opacity that persisted for the entire 14-day observation period. DM's weak ocular irritation at doses known to induce irritation in other sensory tissue is likely a factor contributing to the incorporation of the tearing agent CN in DM riot control preparations.

Gastrointestinal disturbances. DM is classified by the military as a vomiting agent, and several researchers have characterized that response in both humans and laboratory animals.[73,156,157] Although the human studies did not establish the minimal dose of DM required to induce these systemic incapacitating effects, the work did lead to an estimated incapacitating dose of 370 mg•min/m^3. The World Health Organization detailed the progression of symptoms resulting from DM exposure as initial nausea that soon causes violent retching and vomiting.[163] These effects can have an onset after 20 to 30 minutes of exposure.

Other physiological responses. Other systemic effects included headache, mental depression, perspiration, chills, abdominal cramps, and diarrhea.[55,147,161,163–166]

Long-term effects and severe medical complications. Prolonged exposure to DM and/or high-dose acute exposures can cause death by damage to the respiratory tract and lungs, but in general the margin of safety between irritant dose and lethal dose is great.[27] Repeated dose toxicity studies have been conducted in monkeys, dogs, and guinea pigs. Studies of aerosol DM exposures for 10 consecutive days generated by commercial thermal grenades to LCt_{20}, LCt_{25}, and LCt_{50} doses gave little indication of cumulative toxicity. The effect of repeated exposure in humans is not known.

CR (Dibenz*(b,f)*(1,4)oxazepine)

Physical Characteristics and Deployment

CR (CAS: 257-07-8, also called dibenzoxazepine) was first synthesized by Higginbottom and Suschitzkey in 1962. CR is a pale yellow crystalline solid with a pepper-like odor and a molar mass of 195.3, corresponding to a molecular formula of $C_{13}H_9NO$ (Figure 13-11). The molar solubility in water at 20°C is 3.5×10^{-4} mol/L (= ~7 mg/100 mL). The melting and boiling points are 73°C and 355°C, respectively. CR vapor is 6.7 times heavier than air, and the vapor pressure of the solid is 0.00059 mm Hg at 20°C. CR is a stable chemical that may persist for prolonged periods in the environment. It is hydrolyzed very slowly in water. As with CN, washing with soap and water will not inactivate CR, but will remove it from the surface. Compared to CS and CN, CR is the most potent lacrimator with the least systemic toxicity. It is the parent compound of the antipsychotic drug loxapine.[71]

CR is the newest of the C series of RCAs (CN and CR), and no in-use data has been published for this agent. However, an article in *The Observer*, on January 23, 2005, revealed that the British government secretly authorized the use of a chemical RCA in prisons at the height of the Northern Ireland troubles.[167] Documents from 1976, released under freedom of information legislation, show that beginning in 1973 the use of CR was authorized to be used on inmates in the event of an attempted mass breakout. The agent was authorized to be used in the form of an aerosol spray for the personal protection of prison officers, to be fired from water cannons, and also shot in a polyethylene capsule that would spread onto rioters after hitting the security fence. CR was alleged to have been used on October 16, 1974, to quell rioting at Long Kesh prison. The article reported CR's effects to be similar to those of CS, except that it also induces intense pain on exposed skin, and the affected areas remain sensitive for days and become painful again after contact with water.[167]

Physiological Effects

Upshall[168] reported that CR aerosols are very quickly absorbed from the respiratory tract. Following inhalation, the plasma half-life is about 5 minutes, which is about the same following intravenous administration. French et al[169] studied CR metabolism in vitro and in vivo, supporting the previous conclusions that the major metabolic fate of CR in the rat is the oxidation to the lactam, subsequent ring hydroxylation, sulfate conjugation, and urinary excretion.

Clinical Effects

Ballantyne[170] has summarized the mammalian toxicology of CR in various species. The acute toxicity by all routes of exposure (LD_{50} and LCt_{50}) indicates that CR is less toxic than CS and CR.[170] Animals exposed to CR exhibited ataxia or incoordination, spasms, convulsions, and tachypnea. In the exposed surviving animals, these effects gradually subsided over a period of 15 to 60 minutes. Death was preceded by increasing respiratory distress.

Acute effects. Studies at Edgewood Arsenal and other research centers have been conducted to assess the effects of CR on humans following aerosol exposures, drenches, and local application.[134,171–174] The 1984 National Research Council study[60] summarized the human aerosol and cutaneous studies conducted at Edgewood Arsenal from 1963 to 1972. Respiratory effects following aerosol exposures included respiratory irritation with choking and difficulty in breathing or dyspnea; ocular effects consisted of lacrimation, irritation, and conjunctivitis.

Respiratory effects. Ashton et al[171] exposed human subjects to a mean CR aerosol concentration of 0.25 mg/m^3 (particle size: 1–2 μm) for 1 hour. Expiratory flow rate was decreased approximately 20 minutes after the onset of exposure. The investigators theorized that CR stimulated the pulmonary irritant receptors to produce bronchoconstriction and increasing pulmonary blood volume by augmenting sympathetic tone.

The potential of CR aerosols to produce physiological and ultrastructural changes in the lungs was evaluated by Pattle et al.[175] Electron microscopy of rats exposed to CR aerosol of 115,000 mg•min/m^3 did not reveal any effects on organelles such as lamellated osmiophilic bodies. Studies by Colgrave et al[176] evaluated the lungs of animals exposed to CR aerosols at dosages of 78,200; 140,900; and 161,300 mg•min/m^3, and found them to appear normal on gross examination. On microscopic examination, however, the lungs revealed mild congestion, hemorrhage, and emphysema. Electron microscopy showed isolated swelling and thickening of the epithelium, as well as early

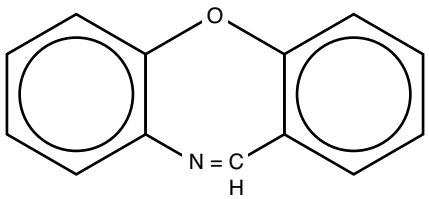

Fig. 13-11. Chemical structure of CR.

capillary damage, as evidenced by ballooning of the endothelium. The authors concluded that these very high dosages of CR aerosols produced only minimal pulmonary damage.

Dermatological effects. CR was reported by Ballantyne and Swanston[134] and by Holland[173] to produce transient erythema, but it did not induce vesication or sensitization and did not delay the healing of skin injuries. The burning sensation on exposure to CR persisted for 15 to 30 minutes, and the erythema lasted 1 to 2 hours.[134,173] Repeated dermal administration of CR was conducted in mice by Marrs et al[177] and in rabbits and monkeys by Owens et al.[178] In the latter study, CR was applied to the skin 5 days per week for 12 weeks. Both teams of investigators concluded that repeated dermal applications of CR had little effect on the skin. They further postulated that in view of the absence of any specific organ effects, absorption of even substantial amounts of CR would have little effect.

Ophthalmologic effects. Higgenbottom and Suschitzky[179] were first to note the intense lacrimation and skin irritation caused by CR. Mild and transitory eye effects such as mild redness and mild chemosis were observed in rabbits and monkeys after a single dose of 1% CR solution. Multiple doses over a 5-day period of the same solution to the eye produced only minimal effects.[179] Biskup et al[180] reported no signs of eye irritation in animals following single or multiple dose applications of 1% CR solutions. Moderate conjunctivitis following the application of 5% CR solution to the eyes of rabbits was reported by Rengstorff et al,[181] although histological examination revealed normal corneal and eyelid tissues. Ballantyne and Swanston[134] also studied the ocular irritancy of CR and arrived at a threshold concentration for blepharospasm in several species. Ballantyne et al[138] studied the effects of CR as a solid, an aerosol, and a solution in polyethylene glycol. Aerosol exposures of 10,800 and 17,130 mg•min/m^3 resulted in mild lacrimation and conjunctival injection, which cleared in 1 hour. When applied in solution, it produced reversible dose-related increases in corneal thickness. The authors concluded that CR produced considerably less damage to the eye than CN and is much safer.

Gastrointestinal disturbances. Although human data is not readily available in this area, animal studies by Ballantyne and Swanston[134] showed the repeated dose effects of orally administered CR on various animal species. The animals that died following intravenous and oral administration demonstrated congestion of the liver sinusoids and alveolar capillaries. At necropsy, the surviving animals did not show any gross or histological abnormalities. The toxic signs following intraperitoneal administration included muscle weakness and heightened sensitivity to handling. These effects persisted throughout the first day following exposure. Some animals also exhibited central nervous system effects. On necropsy, the surviving animals did not show any gross or histological abnormalities.

Other physiological responses. Ballantyne et al[172] reported the effects of dilute CR solution on humans following splash contamination of the face, or facial drench. These exposures resulted in an immediate increase in blood pressure concomitant with decreased heart rate. In subsequent studies by Ballantyne et al,[78] humans were exposed to whole body drenches that resulted in the same effects of immediate increase of blood pressure and bradycardia. The authors concluded that the cardiovascular effects in both studies were caused by the CR, theorizing that the amount of CR uptake was insufficient to produce the systemic effects on the heart. However, they did not provide an explanation for the cardiovascular changes. Lundy and McKay[182] suggested that these cardiovascular changes resulted from the CR effects on the heart via the sympathetic nervous system.

Several animal species were exposed to acute inhalation of CR aerosols and smokes for various time periods. Rats exposed to aerosol concentrations from 13,050 to 428,400 mg•min/m^3 manifested nasal secretions and blepharospasm or uncontrollable closure of the eyelids, which subsided within an hour after termination of the exposure. No deaths occurred during or following these exposures. There were also no deaths in rabbits, guinea pigs, or mice exposed to CR aerosols of up to 68,000 mg•min/m^3. Animals exposed to CR smoke generated pyrotechnically had alveolar capillary congestion and intraalveolar hemorrhage, as well as kidney and liver congestion.

Long-term effects and severe medical complications. Repeated inhalation exposures were conducted by Marrs et al,[183] who exposed mice and hamsters to concentrations of 204, 236, and 267 mg/m^3 CR for 5 days per week for 18 weeks. The high concentrations produced death in both species, but no single cause of death could be ascertained, although pneumonitis was present in many cases. Chronic inflammation of the larynx was observed in mice. Although alveologenic carcinoma was found in a single low-dose and a single high-dose group of mice, the findings and conclusions were questioned because the spontaneous occurrence of alveologenic carcinoma is high in many mouse strains.[184,185] Furthermore, this tumor type differs in many respects from human lung tumors. No lung tumors and no lesions were found in hamsters exposed to CR aerosols. Histopathology revealed hepatic lesions in mice, but these were of infectious origin and not related to the CR. The authors concluded that CR exposures at high concentrations reduced surviv-

ability and that CR produced minimal organ-specific toxicity at many times the human ICt_{50}, which has been reported as both 0.7 mg/m^3 within 1 minute[170] and 0.15 mg/m^3 within 1 minute.[183,186]

Upshall[168] studied the reproductive and developmental effects of CR on rabbits and rats. The animals were exposed to inhalation of aerosolized CR at concentrations of 2, 20, and 200 mg/m^3 for 5 and 7 minutes. Groups of animals were also dosed intragastrically on days 6, 8, 10, 12, 14, 16, and 18 of pregnancy. No dose-related effects of CN were observed in any of the parameters measured or in the number and types of malformations observed. No externally visible malformations were seen in any group, and no dose-related effects of CR were noted in any of the fetuses in any group. Based on the overall observations, the author concluded that CR was neither teratogenic nor embryotoxic to rabbits or rats.

Only one study has reported on the genotoxicity of CR. Colgrave et al[176] studied the mutagenic potential of technical grade CR and its precursor (2-aminodiphenyl ether) in the various strains of *Salmonella typhimurium*, as well as in mammalian assay systems. CR and its precursor were negative in all the assays, suggesting that CR is not mutagenic. Further testing is required to exclude the genetic threat to humans, as well as to determine the carcinogenic potential and its ability to cause other chronic health effects. Husain et al[133] studied the effects in rats of CR and CN aerosols on plasma glutamic oxaloacetic transaminase, plasma glutamic pyruvic transaminase, acid phosphatase, and alkaline phosphatase. The rats exposed to CR exhibited no change in any of these parameters, whereas significant increases in all of these parameters occurred in rats exposed to CN, suggesting that CN can cause tissue damage.

MEDICAL CARE

The effects from RCAs are typically self-limiting, and discomfort is reduced within 30 minutes upon exiting a contaminated area. Usually no medical treatment is necessary, particularly if the agent is used in an open area and the dose is minimized. Medical complications are always possible, however, so emergency services should be prepared to treat a limited number of casualties when RCAs are used for civil disturbance, civilian peacekeeping operations, and training. Injury may range from skin and eye irritation to, in rare cases, injuries sustained from exploding dispensing munitions, delayed transient pulmonary syndromes, or delayed pulmonary edema requiring hospital admission.[4]

Personal Protection

Short-term protection can be provided by dry clothing that covers the arms and legs, because sweat allows dry agents to adhere to the skin. The standard protective mask will adequately protect against the inhalation of RCA particles and vapors. When working with bulk quantities of these agents, or in mask confidence chambers with CS1, CS2, or CR, protective clothing, mask, and gloves that cover all exposed skin areas should be worn.[10] Medical providers do not require protection once an exposed patient has been decontaminated.

Decontamination

Decontamination is important to reduce injury and continued exposure from agent on the skin, hair, and clothing. This is particularly important for those in contact with RCAs in enclosed areas for long periods of time, such as individuals running mask confidence training who are in the chamber repeatedly throughout a single day. CS chamber operators have developed erythema, minor skin burns, and blistering on the neck, arms, and other areas that were not continuously protected by a mask or clothing (Figure 13-12). These problems can be avoided if operators wear adequate dermal protection during exposure and shower immediately with soap and water at the end of the training day.

When dry agents (CS, CR, CN, and DM) are dispensed in the open air in limited quantities, all that is needed to remove the agent, particularly when protective clothing is worn, is brisk movement: flapping the arms and rubbing the hair in a breeze or standing in front of a large fan. This will disperse most of the particles from the clothing and hair. The mask should be worn during this process to insure that particles blown from other people performing the same procedure upwind are not inhaled. However, agent particles adhere to sweaty skin, so completely effective decontamination requires clothing removal followed by thorough washing of exposed skin and hair.

To decontaminate an exposed patient, the contaminated clothing should be removed before admittance to a medical treatment facility. The clothing must be stored in a sealed polythene bag and, if laundered, cold water should be used to reduce vaporization of the agent.[81] Soap and water are an effective decontaminant for RCAs; they will not neutralize the agent but will wash it away. Water should be used in copious amounts. Soap helps loosen the dry particles and

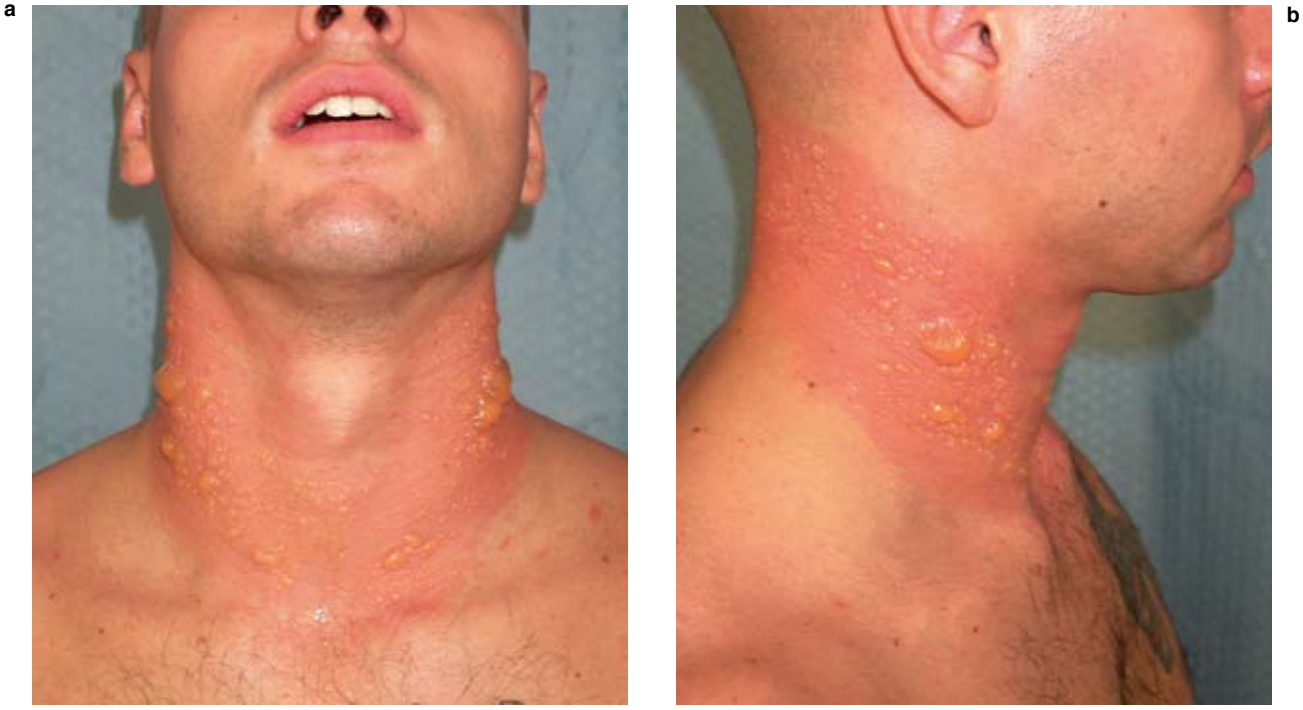

Fig. 13-12. Mask confidence chamber operator after several hours of exposure to concentrated CS. Erythema and blisters are present in areas where the skin was exposed. This service member stated that this is the first time he neglected to shower after training.
Photograph: Courtesy of CG Hurst, US Army Medical Research Institute of Chemical Defense.

remove them adequately from the skin surface. CR, CN and DM hydrolyze very slowly in water, even when alkali is present.[24] Because these agents do not decompose in water, washing with soap and water will only remove them from surfaces. Run-off may produce irritation if it gets into the eyes, so the eyes should be closed and head lowered during decontamination (if the agent is not already in the eyes). Environmental contamination from these agents may be persistent and difficult to remove. CS is insoluble in water but will hydrolyze in water at a pH of 7, with a half-life of approximately 15 minutes at room temperature, and extremely rapidly in alkaline solution with a pH of 9, with a half-life of about 1 minute.[71]

Decontamination solutions used on human skin should not be caustic to the skin. A solution containing 6% sodium bicarbonate, 3% sodium carbonate, and 1% benzalkonium chloride was found to bring prompt relief of symptoms and to hydrolyze CS.[187] No form of hypochlorite should ever be used to decontaminate CS or other RCAs because it can react with CS to produce more toxic chemical byproducts and will further irritate tissues.[51] Applying water or soap and water to skin exposed to CS or OC but decontaminated may result in a transient worsening of the burning sensation, which should dissipate with continued water flushing.[3,10] PS liquid can also be decontaminated with soap and water, and clothing, which can trap vapor, should be removed.[188]

Water in limited quantities increases the pain symptoms from OC, which has a water solubility of 0.090 g/L at 37° C.[24,189] Without decontamination, OC symptoms should dissipate over time as the body's substance P is diminished. OC resin can also be decontaminated with copious amounts of water, liquid soap and water, baby shampoo, alcohol, or cold milk.[22] OC in the eyes can be decontaminated with copious water flushing, but symptoms may not dissipate for 10 minutes. A compress of cold milk, ice water, or snow can help reduce the burning sensation once the individual has been decontaminated.[22] Substances with high fat content, such as whipped cream or ice cream, also aid in decontamination and help reduce pain.[22] Although OC is soluble in vegetable oil and other hydrocarbons, and such solutions can more easily be washed off the skin, hydrocarbons must not be used with solutions of OC and other RCAs such as CN.[24,190] Commercially available products, such as Sudecon Decontamination Wipes (Fox Labs International, Clinton Township, Mich); Bio Shield towelettes (Bio Shield, Inc, Raleigh,

NC); or Cool It! wipes and spray (Defense Technology, Casper, Wyo); claim to help decontaminate and reduce pain in people exposed to pepper sprays and other RCAs.[191–193]

Treatment

Skin

Skin erythema that appears early (up to 1 hour after exposure) is transient and usually does not require treatment. Delayed-onset erythema (irritant dermatitis) can be treated with a bland lotion such as calamine lotion or topical corticosteroid preparations (eg, 0.10% triamcinolone acetonide, 0.025% fluocinolone acetonide, 0.05% flurandrenolone, or betamethasone-17-valerate). Cosmetics, including foundation and false eyelashes, can trap agent and should be removed to insure complete decontamination.[22] When the patient has been exposed to OC, the use of creams or ointments should be delayed for 6 hours after exposure.[194] Patients with blisters should be managed as having a second-degree burn.[195] Acute contact dermatitis that is oozing should be treated with wet dressings (moistened with fluids such as 1:40 Burow solution or colloidal solution) for 30 minutes, three times daily.[3,187] Topical steroids should be applied immediately following the wet dressing. Appropriate antibiotics should be given for secondary infection, and oral antihistamines for itching. [3,187] Vesicating lesions have been successfully treated with compresses of a cold silver nitrate solution (1:1,000) for 1 hour, applied six times daily.[75] One person with severe lesions and marked discomfort was given a short course of an oral steroid. An antibiotic ointment was applied locally, but systemic antibiotics were not used.[75] With severe blistering resulting in second-degree burns, skin pigmentation changes can occur.[4]

Eye

The effects of RCAs on the eyes are self-limiting and do not normally require treatment; however, if large particles of solid agent are in the eye, the patient should be treated as if for exposure to corrosive materials.[195] The individual should be kept from rubbing the eyes, which can rub particles or agent into the eye and cause damage.[24] Contact lenses should be removed.[194]

Yih recommends that before irrigating eyes contaminated with CS, they should be blown dry, directly, with an electric fan, which helps dissolved particles evaporate and rapidly reduces pain (irrigating the eyes before drying causes additional, unnecessary, pain.[82] However, other researchers note that if Yih's recommendations are used, the care provider must be certain that the agent is CS, for such a delay in decontaminating more toxic agents such as ammonia would result in severe eye injury. With all agents, the affected eyes should be thoroughly flushed with copious amounts of normal saline or water for several minutes (some sources suggest 10 minutes) to remove the agent.[194]

Eye injury assessment should include a slit lamp examination with fluorescein staining to evaluate for corneal abrasions that could be caused by rubbing particles of the agent into the eye.[4,196] Patients should be closely observed for development of corneal opacity and iritis, particularly those who have been exposed to CN or CA. A local anesthetic can be used for severe pain, but continued anesthetic use should be restricted. If the lesion is severe, the patient should be sent for definitive ophthalmologic treatment.

Viala et al[197] reported a study of five French gendarmes who had CS exposure and were decontaminated with Diphoterine (Prevor, Valmondois, France), which dramatically resolved the effects in four of them. The researchers also recommended using it as a prophylaxis to reduce or prevent lacrimation, eye irritation, and blepharospasm.[197]

Respiratory Tract

Typically, RCA-induced cough, chest discomfort, and mild dyspnea are resolved within 30 minutes after exposure to clean air. However, both the animal data (detailed in the section on CS) and clinical experience with an infant exposed to CS[198] suggest that severe respiratory effects may not become manifest until 12 to 24 hours after exposure. If persistent bronchospasm lasting several hours develops, systemic or inhaled bronchodilators (eg, albuterol 0.5%) can be effective in reducing the condition.[4,196]

Individuals with prolonged dyspnea or objective signs such as coughing, sneezing, breath holding, and excessive salivation should be hospitalized under careful observation. Treatment in these cases may include the introduction of systemic aminophylline and systemic glucocorticosteroids.[4,55] A chest radiograph can assist in diagnosis and treatment for patients with significant respiratory complaints.[196] If respiratory failure occurs, the use of extracorporeal membrane oxygenation can be effective without causing long-term damage to the lungs.[4,199] High-pressure ventilation, which can cause lung scarring, should not be used. Although people with chronic bronchitis have been exposed to RCAs without effects, any underlying lung disease (eg, asthma, which affects one person in six) might be exacerbated by exposure to CS.[3,200] In most cases the

respiratory system quickly recovers from acute exposure to RCAs, but prolonged exposure can predispose the casualty to secondary infections. Further care should be as described in Chapter 10, Toxic Inhalational Injury and Toxic Industrial Chemicals.

Cardiovascular System

Transient hypertension and tachycardia have been noted after exposure to RCAs, primarily because of the anxiety or pain of exposure rather than a pharmacological effect of the compound.[201] Whatever the cause, adverse effects may be seen in individuals with hypertension, cardiovascular disease, or an aneurysm.

Laboratory Findings

No specific laboratory study abnormalities are helpful in diagnosing RCA exposure. Appropriate tests can be ordered to guide treatment if respiratory tract or skin infection is suspected. Arterial blood gasses can be ordered if there is a concern about adequate ventilation.[196]

NEW DEVELOPMENTS AND FUTURE USE

As documented throughout this chapter, the military's interest in and occasional use of RCAs has not only kept pace with their development, but in many cases the military has spearheaded the effort. Although most of this historical activity predated the current regulations guiding research, development, and use of RCAs (ie, prior to the Chemical Weapons Convention), it is probable that this trend will continue into the future.

Recent years have witnessed a fundamental methodological shift in biomedical science research. The traditional method of identifying biologically active compounds before determining their application to disease has been replaced, in part, by identifying biological targets (ie, protein receptors) first, followed by identifying the chemical compounds capable of binding to the targets and altering their function. The advancement of microarray, proteomics, toxicogenomics, database mining techniques, and computational modeling techniques has greatly accelerated the ability to identify novel biological targets with desired physiological effects. Likewise, high-throughput technologies capable of identifying biologically active compounds such as in-vitro tissue culture systems integrated with automated robotics test stations, combinatorial chemistry, and quantitative structure activity relationship methods have accelerated new drug discovery. New RCAs are likely to be a product of this research.

Neuropharmacology is an area of biomedical research likely to yield future RCAs. The increased incidence and awareness of neurological disorders in the general population, such as Alzheimer disease in the elderly and attention deficit disorders in children, ensure a healthy research base aimed at discovering bioactive compounds capable of altering cognitive functions, perception, mood, emotions, bodily control, and alertness.

Although OC and CS, today's RCAs of choice, are very safe if deployed appropriately, more research is needed to illuminate the full health consequences of their use. The limited financial resources of the military's chemical defense programs dictate that funds be spent on measures to defend against more lethal chemical agents and toxins that could be used by America's enemies. Law enforcement agencies and manufacturers also have limited resources to thoroughly investigate the safety of these compounds. Currently, federal resources are more wisely used to prevent disease and address healthcare issues that affect the population at large.

The control of the administration of RCAs might be difficult to regulate, particularly in the areas and under the circumstances in which the use of RCAs has apparently been misused (eg, the West Bank and Gaza Strip, and Seoul, South Korea). Despite the concern about the occasional loss of life of those exposed to RCAs or the occasional injury among innocent bystanders, there is serious doubt that a prohibition of the use of RCAs would be effective. Although in some instances dialogue and negotiation should precede the use of RCAs, these agents have proved effective in curbing damage to property and persons in threatening situations. Although RCAs sometimes cause permanent injury or death, especially when used in enclosed spaces or against those with existing cardiopulmonary compromise, in most situations the amount of injury is small compared to what might have happened if more extreme measures (physical or lethal force) had been used.

SUMMARY

RCAs are intended to harass or to cause temporary incapacitation. The intended target might be rioters in a civil disturbance, or if approved by the president of the United States, the military in an armed conflict. Although developed to have a high margin of safety, RCAs can cause injury or death when used in spaces

without adequate ventilation for prolonged periods, deployed incorrectly, or used against those with pre-existing medical conditions. Although injuries such as burns or fragment penetration can also result from the exploding delivery device rather than from the actual agent, these injuries should not be confused. Data show that RCAs such as OC and CS are safe when used for their intended purpose.

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