
11 Riot-Control Agents

Harry Salem, Eugene J. Olajos, and Sidney A. Katz

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I. INTRODUCTION

Riot-control agents, chemicals that produce disabling physiological effects when they come in contact with the eyes or skin or when inhaled, are a subset of a larger group of chemicals known as "harassing agents." These compounds have the capability of causing intense sensory irritation and marked irritation of the skin and mucous membranes of the eye and respiratory tract. Riot-control agents are peripheral sensory irritants and are collectively referred to as lacrimators. In common parlance they are known as "tear gases." Peripheral sensory irritants are substances that pharmacologically interact with sensory nerve receptors in skin and mucosal surfaces at the site of contamination, resulting in local sensation (discomfort or pain) with associated reflexes. This is a normal biological response giving warning and protective functions. For example, in the eye, sensory irritation results in pain in the eye (warning) and excess reflex lacrimation and blepharospasm (protection). The response is usually concentration-related and disappears on removal of the sensory irritant stimulus. The intense lacrimation best typifies the biological response to such compounds; however, it must be kept in mind that riot-control compounds have multiple physiological effects. A lacrimatory compound may also elicit pulmonary irritation and/or nausea and vomiting. Generally, classification of military chemicals and chemical agents is based on a salient physiologic action although classification may also be based on use, physical state, or persistency.¹⁻⁴ Sartori was of the opinion that the physiological classification of chemical agents and military chemicals, although widely used, was less exact than other classification schemes.⁴ He long ago suggested that classification should be based according to the mechanism of action on the organism.

Physiologically, riot-control agents may be classified as to type: lacrimators, which primarily cause eye irritation and lacrimation; vomiting agents, which additionally cause vomiting; and sternutators, which mainly cause uncontrollable sneezing and coughing. Riot-control agents have also been referred to as irritants or irritating agents,^{5,6} harassing agents,⁷⁻¹⁰ and incapacitating agents or short-term incapacitants.⁹⁻¹¹ The aforementioned categories are general classifications or have special meaning in terms of military usage and may not represent useful equivalents. As a case in point, Cookson and Nottingham are of the opinion that vomiting agents are incorrectly described as riot-control agents and should be considered as a separate

category of military chemicals.¹² Furthermore, it must be recognized that physiologically based classification of chemical agents and compounds of military interest is by no means a rigid one—i.e., the classifying of a military compound, as a lung irritant for instance, does not mean it cannot act as a lacrimatory compound. The issue of classification may never be fully resolved; however, a system of classification nevertheless serves to provide some sort of basis for comparison of chemical agents and compounds. The reader is referred to an excellent overview by Verwey concerning criteria to distinguish riot-control agents from chemical warfare agents, as well as a discussion focusing on the concepts of “harassing,” “irritating,” and “incapacitating.”¹³ Characteristics common to riot-control agents are: (1) a rapid onset of effects; (2) a relatively short duration of effects after cessation of exposure; and (3) a relatively high safety ratio. Ideally, riot-control agents should produce “harassing effects” that are relatively benign with a low incidence of casualties in riot-control situations. They should have very low acute toxicity and possess physical and toxicological properties that ensure minimal risks.

A distinction has been made between chemical warfare agents and military chemicals and is recognized in military field and technical manuals and in chemical warfare literature. The term military chemical compound excludes chemical warfare agents. Chemical warfare agents include the following categories: nerve agents [e.g., sarin (GB), soman (GD), and VX]; blister agents [e.g., mustard (HD) and lewisite (L)]; choking agents/lung irritants [i.e., phosgene (CG)]; blood agents [e.g., hydrogen cyanide (AC) and cyanogen chloride (CK)]; and incapacitating agents [e.g., adamsite (DM) and 3-quinuclidinyl benzilate (BZ)]. Military chemical compounds include the following groupings: riot-control agents [e.g., chloroacetophenone (CN), dibenz (b,f)-1:4 oxazepine (CR), and o-chlorobenzylidene malononitrile (CS)]; training agents [e.g., CN]; smoke materials [e.g., fog oil (SGF) and white phosphorus (WP)]; and herbicides [e.g., 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) and arsenic trioxide]. Further to this discussion, it should be stated that the United States does not consider riot-control agents to be chemical weapons; however, some other countries do not draw such a distinction. Official American sources such as military field and technical manuals (i.e., Army FM 8–285) provide definitions for chemical agent, military chemical, and riot-control agent.¹⁴ Sidell, in writing about riot-control agents, refers to the United States’ position on these compounds and states the following: “The United States does not recognize riot-control agents as chemical warfare agents as defined in the Geneva Convention of 1925.”¹⁵ Despite considerable focus and debate on the definition and classification of riot-control agents, recently published literature on the subject matter has not provided clear distinctions on the classification of chemical warfare agents and riot-control compounds.^{11,16} Nonetheless, the currently held official policy on riot-control agents by the United States is that riot-control agents are not chemical warfare agents.¹⁷

II. HISTORICAL PERSPECTIVES

Lacrimatory and irritant compounds, with a history dating from World War I, have been used in riot-control and civil disturbances, military exercises and training, and as chemical warfare agents. A listing of these chemicals and their use application is

presented in Table 11.1. Chloropicrin (trichloronitromethane, Green Cross, PS) was a well-known chemical substance prior to World War I, having been first synthesized circa 1850. It was used both as a harassing agent and lethal chemical in the First World War. In fact, chloropicrin was one of several lethal agents—the others being chlorine, phosgene, and trichlorethylchloroformate. Adamsite (DM, diphenylaminochlorarsine), an arsenic-based compound, was developed as a chemical variation of diphenylchloroarsine for use during World War I. It is classified militarily as a vomiting agent and as a sternutator and was used as a riot-control agent after the war. According to Swearengen, ethyl bromoacetate was the first riot-control agent, based on its use in Paris in 1912.¹⁸ This tear gas was again utilized in the 1970s.¹⁹ Tear gases used in World War I included such chemicals as acrolein (papite), bromoacetone (BA,B-stoff), bromobenzyl cyanide (BBC,CA), chloroacetone (A-stoff), diphenylaminochloroarsine (DM), and xylol bromide (T-stoff). Xylol bromide was an early war gas, and bromoacetone, a highly potent lacrimator, was the most widely used lacrimatory agent in World War I. Chloroacetophenone (“mace”),* discovered in 1871, was not used during World War I; however, American investigators were certain of its potential utility as a tear gas and worked out a satisfactory process of manufacture.

Military experience with harassing agents encouraged the utilization of these compounds in law enforcement operations. However, many of the military harassing agents are not suited to law enforcement use either, because the risk of fatalities or the likelihood of total incapacitation is too great. The development of modern riot-control agents has been driven by the need to develop safe and effective compounds that can be easily disseminated. Riot-control agents are intended to simply temporarily disable—the intense irritant effects lead to a more or less pronounced incapacitation. Further discussion on “incapacitating” effects of riot-control agents can be found in the literature.^{12,20–22} A systematic search of candidate compounds suitable for riot control and temporary incapacitation was in place at the conclusion of World War I. Despite the evaluation of a considerable number of candidate compounds, interest still centered on CN, DM, and a handful of promising compounds such as CR and CS. The war gas bromobenzyl cyanide (BBC, CA) saw early use as a riot-control agent. However, CN and DM were the harassing agents of choice and, at the time of World War II, considerable stockpiles of CN and DM existed. Although adamsite (DM) has been used as a riot-control agent,¹ chloroacetophenone (CN) became the lacrimator of choice for police use. Chlorobenzylidene malononitrile (CS), synthesized in the late 1920s by Corson and Stoughton, was not developed as a riot-control agent until the 1950s.²³ CS has largely replaced CN and is the tear gas (lacrimator) most widely used by law enforcement personnel. Dibenz(b,f)1:4-oxazepine (CR), a riot-control agent of relatively recent origin, is used only to a very limited extent. However, it may see greater use because CR has greater potency and lower toxicity than some of the other riot-control agents. The compound 1-methoxy-,3,5-cycloheptatriene (tropilidene, CHT), a highly volatile and unstable

*Mace® is a liquid mixture containing CN (active ingredient), hydrocarbons, and freon propellant in 1,1,1-trichloroethane.

TABLE 11.1
Lacrimary Agents and Irritants: Application/Use Information

Chemical	Synonyms	Code ^a	Application/Use	
			Current	Former
σ -Chlorobenzylidene malononitrile	2-Chlorobenzalmononitrile	CS	Riot control	Riot control
Dibenz (b,f)-1:4 oxazepine	CR	CR	Riot control	Riot control
ω -Chloroacetophenone	2-Chloroacetophenone	CN	Riot control	War gas
Diphenylaminochloroarsine	10-Chloro-5,0-dihydro-phenarsazine	DM	Obsolete	War gas
Acrolein	2-Propenal	Papite	Intermediate ^b	War gas
Benzyl bromide	1-Bromotoluene	(–)	Intermediate ^c	Intermediate
Benzyl iodide	1-Iodotoluene	(–)	Reagent	Experimental tear agent
Bromoacetone	1-Bromo-2-propanone	BA	Reagent	War gas
Bromobenzyl cyanide	α -Bromo- α -tolunitrile	BBC	Agricultural chemical	Riot control
Chloroacetone	1-Chloro-2-propanone	A-stoff	Intermediate ^b	War gas
Chloropicrin	Trichloronitromethane	PS	Fumigant war gas	
Ethyl bromoacetate	Ethyl 2-bromoacetate	EBA	Intermediate ^d	Riot control
Ethyl iodoacetate	Iodoacetic acid, ethyl ester	KSK	Reagent	Experimental tear gas
Iodoacetone	1-iodo-2-propanone	(–)	Reagent	Experimental tear gas
Oleoresin of capsicum	OC pepper spray	(–)	Food additive incapacitant	Food additive
Phenyl carbylamine chloride	Phenylimidocarbonyl chloride	(#) ^e	Reagent	War gas
Tropilidene	1-Methoxy-1,3,5-cycloheptatriene _cycloheptatriene	CHT	Experimental tear gas	Experimental tear gas
Xylol bromide	α -Bromoxylene	T-stoff	Reagent	War gas

^aMilitary code or identifier.

^bChemical intermediate for various industrial chemicals and pharmaceuticals.

^cChemical intermediate for certain industrial chemicals.

^dChemical intermediate for pharmaceuticals.

^e(#) Military designation = Green Cross I.

liquid, has also been studied and evaluated as a riot-control agent. Tropilidene has been demonstrated to be a potent irritant with physiological effects characteristic of riot-control agents. Its toxicity is generally similar to that of CR. The naturally occurring compound capsaicin may have potential use as a riot-control agent—"pepper spray" is currently available over the counter for personal protection and is used by postal carriers for repelling animals, and by campers as a bear repellent.

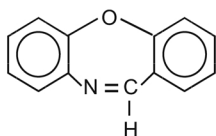
III. CHEMISTRY OF SELECTED RIOT-CONTROL AGENTS

A considerable number of chemicals have been developed for riot control and law enforcement use. The most commonly available riot-control agent is chlorobenzylidene malononitrile (CS), which replaced chloroacetophenone (CN), the latter agent having replaced adamsite (DM). Oleoresin capsicum (OC), in various formulations, has gained popularity in law enforcement and riot-control use. The structures of riot-control agents CS, CR, CN, and DM are depicted in Figure 11.1, and Table 11.2 summarizes selected physicochemical properties of several lacrimatory agents. The common riot-control agents are all solids in pure form, although lacrimatory agents such as acrolein, chloroacetone, and tropilidene, which have been considered and/or used for riot control, are liquids. Of the modern riot-control agents, CS hydrolyzes rather rapidly; however, other compounds such as dibenz (b,f) 1:4-oxazepine (CR) are particularly stable and persist for prolonged periods. The common riot-control agents are alkylating agents that react with nucleophilic sites of macromolecular moieties. A brief description of the chemico-physical properties of the common riot-control agents is presented in Table 11.2.

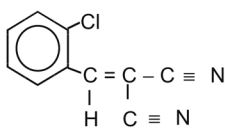
A. CHLOROBENZYLIDENE MALONONITRILE (CS)

Chlorobenzylidene malononitrile has the military designation CS. It is also known as β,β -dicyano-ortho-chlorostyrene, 2-chlorophenylmethylenepropanedinitrile, and o-chlorobenzal malononitrile. CS is a white solid with a molar mass of 188.5 corresponding to a molecular formula of $C_{10}H_5N_2Cl$. The molar solubility in water at 20°C

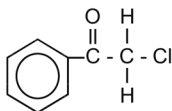
dibenz (b,f) - 1:4 - oxazepine (CR)



2 - chlorobenzylidene malononitrile (CS)



1 - chloroacetophenone (CN)



10 - chloro - 5,10 - diphenylarsazine (DM)

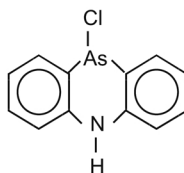


FIGURE 11.1 Structures of CS, CR, CN, and DM.

TABLE 11.2**Selected Chemical and Physical Properties of Lacrimatory Agents**

Compound	CS	CR	CN	OC ^a	DM	CA	PS
Molecular Wt	188.5	195.3	154.5	(-)	277.5	196.0	164.5
Melting Point	93°C	72°C	54°C	(-)	195°C	25.5°C	-69°C
Vapor Pressure	0.00034	0.00059	0.0054	(-)	2×10^{-13}	0.011	18.3
Volatility	0.71/25	0.63/25	1.06/52	(-)	(-)	271/30	(-)
Solubility	IOC	IOC	IOC	(-)	IO	IO	IO
Hydrolysis	Slow	V. slow	Slow	(-)	Inhibited	Slow	None

Note: CS = o-chlorobenzylidene malononitrile; CR = dibenz-(b,f)-1:4 oxazepine; CN = chloroacetophenone; OC = oleoresin capsicum; DM = adamsite; CA = bromobenzylcyanide; PS = chloropicrin. Vapor pressure at 20°C (68°F) (mmHg). Volatility, mg/m³/°C for other than 20°C. Solubility, I = limited in water, O = soluble in organics, C = soluble in chlorinated organics. Hydrolysis (rate of hydrolysis). (-) Denotes no value.

^aOleoresin capsicum is a mixture—no values.

is 2.0×10^{-4} mol/l (= ~4 mg/100 ml). Dissolved CS is rapidly hydrolyzed; however, CS may persist in the environment because its solubility in water is limited. The melting and boiling points are 93–96°C and 310–315°C, respectively. The vapor is several times heavier than air, and the vapor pressure of the solid is 0.00034 mm Hg at 20°C.

B. DIBENZ (B,F)1:4-OXAZEPINE (CR)

The military designation for dibenz (b,f) 1:4-oxazepine is CR. This compound is a pale yellow solid with a molar mass of 195.3 corresponding to a molecular formula of C₁₃H₉ON. 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 72°C and 335°C, respectively. The 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 and may persist for prolonged periods in the environment.

C. CHLOROACETOPHENONE (CN)

Chloroacetophenone is also referred to as ω-chloroacetophenone, α-chloroacetophenone, phenacyl chloride, 2-chloro-1-phenylethanone, and phenyl chloromethyl ketone. It has the military designation CN. Chloroacetophenone is a white solid with a molar mass of 154.5 corresponding to a molecular formula of C₈H₇OCl. The molar solubility at 20°C is 4.4×10^{-3} mol/l (= 68 mg/100 ml). Melting and boiling points are 54°C and 247°C, respectively. Density of the solid is 1.318 g/cm³ at 0°C, and density of the liquid is 1.187 g/m³ at 58°C. The vapor is 5.3 times heavier than air. The vapor pressure of the solid is 2.6×10^{-3} torr at 0°C, 4.1×10^{-3} torr at 20°C, and 15.2×10^{-3} torr at 50°C.

D. OLEORESIN CAPSICUM (OC)

Oleoresin capsicum is a reddish-brown, oily liquid obtained by extracting dried, ripe fruit of chili peppers, usually *Capsicum annuum* or *Capsicum frutescenes*. Oleoresin capsicum is a mixture of many compounds. Its composition is variable and depends on factors such as maturity of the fruit and the environment in which the plants are grown, as well as the conditions of the extraction. More than 100 compounds have been identified in oleoresin capsicum. Among the branched- and straight-chain alkyl vanillylamides isolated from oleoresin capsicum, capsaicin (8-methyl-N-vanillyl-6-noneanamide) is the major constituent. Capsaicin is the major pungent component in many peppers, and it is particularly noted for its irritant properties. Depending on the variety of chili pepper, oleoresin capsicum contains from 0.01 to 1.0% capsaicinoids on a dry mass basis. Some of the capsaicinoids found in oleoresin capsicum are capsaicin (~70%), dihydrocapsaicin (~20%), norhydrocapsaicin (~7%), homocapsaicin (~1%), and monodihydrocapsaicin (~1%). Other components of oleoresin capsicum may also possess irritant properties (e.g., phenolic compounds, acids, and esters).

E. ADAMSITE (DM)

Diphenylaminochloroarsine (phenarsazine chloride, adamsite) has the military designation, DM. Adamsite is a yellowish and odorless solid that is very stable in pure form. The melting point is 195°C, and the vapor pressure is negligible (2×10^{-13} mm Hg at 20°C). As a solid, the rate of hydrolysis is not significant, owing to the formation of an oxide coating; however, the rate of hydrolysis is rapid when as an aerosol. DM has a molecular weight of 277.5 with the formula $C_6H_4(AsCl)(NH)C_6H_4$.

IV. CLINICAL ASPECTS OF RIOT-CONTROL AGENTS

Riot-control agents exert their effects on eyes and skin and can enter the body via the respiratory tract, skin, and gastrointestinal tract. The clinical symptoms following exposure to riot-control agents are the consequence of these agents' ability to cause intense sensory irritation. Most of the symptoms are felt within 10 to 30 s. The eyes are affected almost immediately with copious lacrimation, blepharospasm, conjunctivitis, and pain. Nasal effects include rhinorrhea, itching, and pain. A stinging or burning sensation of the mucosal surfaces is also experienced. Sneezing, coughing, and increased respiratory tract secretions are accompanied by a burning sensation and chest tightness. There is a burning sensation of the skin followed by erythema. The more severe effects such as marked coughing, retching, and vomiting may occur if an individual remains in a riot-control agent atmosphere following the onset of irritation. Anxiety and panic are reactions that are commonly noted on exposure to these compounds. The intense physical discomfort and anxiety can produce cardiovascular changes such as increased blood pressure. After cessation of exposure, most symptoms persist for a brief period, and by 30 min, most symptoms have completely abated. Conjunctivitis can remain for up to 30 min. On exposure to massive doses, which can be achieved with aggressive use of certain riot-control agents such as CN, severe effects involving the eyes (i.e., corneal damage) and lungs (e.g., hemorrhaging,

edema, and congestion) can result. These agents may also complicate and exacerbate existing conditions such as bronchitis and asthma.

V. TOXICOLOGY OF RIOT-CONTROL AGENTS

Riot-control agents are potent sensory irritants of low toxicity that produce dose- and time-dependent acute, site-specific toxicity (refer to [Figure 11.2](#) and [Tables 11.3](#) and [11.4](#)). These agents have been described as non-lethal. Exposures to these compounds involve the ocular, inhalation, and cutaneous routes and indirectly via the oral route. These compounds primarily act on the eye, which is the most sensitive target organ; however, most of these compounds will also cause effects involving the respiratory tract and skin. These agents can cause several or all of the effects on these target organs to a greater or lesser extent. The immediate effects on exposure to riot-control agents are: intense irritation of the eyes; marked irritation of the nose, throat, and lungs; and irritation of the skin. The margin of safety between the amount eliciting an intolerable effect and that which may cause serious adverse effects is large. For example, the lethal amount for the riot-control agent CS is estimated to be 2600 times as great as the dosage required to cause temporary disabling, and that of bromobenzyl cyanide is 3000 times as great. Riot-control agents are not usually accompanied by permanent toxic effects, although the risks for deleterious effects, longer-term sequelae, or even death increase with higher exposure concentrations and greater exposure duration. Overall, the acute and short-term repeated toxicity of riot-control agents is well characterized; however, the extent of our knowledge regarding long-term and chronic effects on exposure to some of these compounds is somewhat limited. The animal and human toxicology of the main riot-control agents (CN and CS), along with CR, DM, and capsaicin is presented; each agent will be considered separately. Topics covered are comparative toxicology, dose-effect relationships, target organ effects, low-dose toxicity, biochemistry, and mechanism(s), as well as consideration of the effects in susceptible subpopulations.

VI. OCULAR AND CUTANEOUS EFFECTS OF RIOT-CONTROL AGENTS

Many compounds possess more or less lacrimatory properties that vary in intensity from mild to severe irritation, with copious flow of tears. The most characteristic feature of riot-control agents is their ability to cause immediate stinging sensation in the eyes with tearing (stimulatory effect) at low concentrations that results in a temporary disabling effect. These compounds produce stinging and lacrimation and reversible and non-injurious effects at low concentrations; however, at high concentrations, ocular damage can result with some irritants. Moderate injury to the eyes following exposure to riot-control agents consist of corneal edema, which is reversible. More serious injurious action of riot-control agents may include corneal opacification, vascularization and scarring of the cornea, and corneal ulceration. Lacrimatory agents that have been associated with ocular injury, for example, include chloroacetophenone (CN), chloracetone, and bromobenzyl cyanide. Ocular injuries are more prevalent

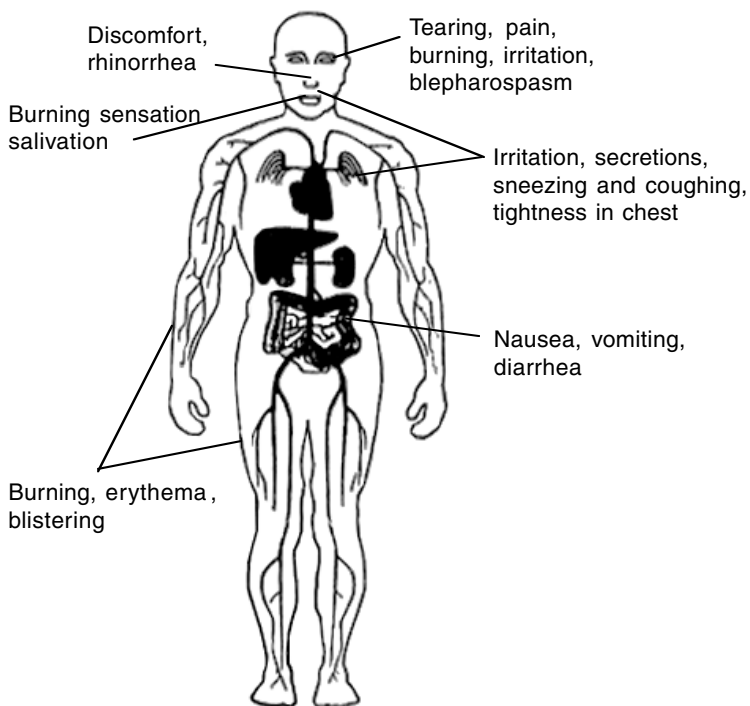


FIGURE 11.2 Site-specific toxicity of riot control agents (human body).

TABLE 11.3
Comparative Toxicity of Lacrimatory Compounds: Human Estimates^{1,2,4,6,12,15,105}

Compound	LC _{t50} (mg-min/m ³)	IC _{t50} (mg-min/m ³)	Minimal Irritant ConC(mg-min/m ³)
CN	8500—25000	20—50	0.3—1
CR	>100000	~1	0.002
CS	25000—150000	5	0.004
DM	11000—35000	20—150	1—5
Acrolein	3500—7000	(—)	2—7
Bromobenzyl cyanide	8000—11000	30	0.3
Chloroacetone	>3000	(—)	18
Chloropicrin	2000	(—)	2—9
Xylyl bromide	5600	(—)	~5
Capsaicin	(—)	(—)	(—)

Note: When more than one estimate has been reported, a range is given; (—) denotes value not determined.

TABLE 11.4

Comparative Toxicity (LD₅₀) and LCt₅₀) of CR^a, CS^b, and CN^b

Route	Species	LD ₅₀ (mg/kg) ^c		
		CR	CS	CN
i.v.	Mouse	112	48	81
	Rat	68	28	40
	Rabbit	47	27	29
i.p.	Rat	766	48	38
	Guinea pig	463	73	17
Oral	Mouse	4000	(-)	(-)
	Rat	5900	1284	52
	Rabbit	1760	142	118
	Guinea pig	629	212	157
		LCt ₅₀ (mg-min/m ³) ^c		
		CR	CS	CN
Inhalation				
Pyrotechnically generated	Mouse	203,600	76,000	(-)
	Rat	139,000	68,000	23,000
	Rabbit	160,000	63,000	15,800
	Guinea pig			
Aerosol	Mouse	169,500	67,200	18,200—73,500 ^d
	Rat	428,400	88,460	3,700—18,800 ^d
	Rabbit	169,000	54,100	5,840—11,480 ^d
	Guinea pig	169,500	50,010	3,500—13,140 ^d

Note: (-) Denotes no data; i.v. = intravenous; i.p. = intraperitoneal.

^a Data from several sources as reported by Ballantyne.²⁴

^b Data from several sources as documented in a report by the NAS.⁶

^c Lowest value reported.

^d Range of values from several sources.

following use of explosive (thermal type) tear gas devices, as contrasted to solvent spray-type tear gas devices. A description of the differences between thermal and solvent spray-type devices has been provided by MacLeod.²⁵ Reviews regarding riot control agent-induced ocular injury have been published.^{25–30} The comparative ocular irritancy of various lacrimogenic compounds is presented in Table 5. Ocular effects are described in greater detail for each of the main riot-control agents.

Although the eyes and respiratory tract are the primary organs affected by riot-control agents, the skin is also often involved. Riot-control agents are primary irritants that in low concentrations produce tingling or burning sensation and transient

TABLE 11.5**Human Ocular Irritancy and Toxicity of Lacrimatory Compounds**^{1,2,4,6,10,12,15,24,105}

Compound	Ocular Irritancy	Onset of Action Threshold (mg/m ³)	Irritancy ^a	Intolerable Conc. (mg/m ³)	Lethal Conc. (mg/m ³)
CN	Profound	Immediate	0.3	5–30	850
CR	Profound	Immediate	0.002	~1	10000
CS	Profound	Immediate	0.004	~3	2500
DM	High	Rapid	~1	5	650
Acrolein	High	Rapid	2–7	50	350
Benzyl bromide	High	Rapid	4	50	4500
Bromobenzyl cyanide	Profound	Rapid	0.15	0.8	350
Chloroacetone	High	Rapid	18	100	2300
Chloropicrin	High	Rapid	2–9	50	2000
Xylyl bromide	High	Rapid	~5	15	5600
Capsaicin	High	Rapid	(–)	(–)	(–)

^aA range is given when more than one value has been reported.

^bMinimum lethal concentration for 10-min exposure.

erythema. At higher concentrations, agents such as CN, CS, and DM can cause edema and blistering. In addition, riot-control agents can produce allergic contact dermatitis after an initial exposure. The effects of riot-control agents on the skin are successfully treated with topical steroid preparations and oral antihistamines for itching. Appropriate antibiotics are administered to treat secondary infection.

VII. SPECIFIC RIOT-CONTROL COMPOUNDS

A. O-CHLOROBENZYLIDENE MALONONITRILE (CS)

The riot-control agent o-chlorobenzylidene malononitrile, commonly known as CS, is named after the initials of the two British chemists who prepared it in 1928, Corson and Stoughton.²³ In the 1950s, CS was developed as a potent and safe riot-control agent. The United States Army adopted CS as its standard riot-control agent in 1959. CS has been extensively studied in animals and humans, and has been widely used around the world with no verified deaths in humans following its use. CS, like CN and DM, is a crystalline, solid substance that is soluble in organic solvents, but poorly soluble in water. These compounds can be disseminated as dry powders, by thermal or explosive methods, via spraying of the molten materials or in solution with organic solvents. CS2, a micronized formulation of CS, consists of 95% CS, 5% Cab-o-Sil® (Cabot Corp) and 1% hexamethyldisilazane. The additives prevent agglomeration and produce a free-flowing powder, which can be dispersed in the dry form.³¹

1. Mammalian Toxicology

CS is a sensory irritant, highly irritating to mucous membranes that cover or line tissues of the eyes, nose, throat, and stomach. Irritation of the eyes may cause pain, excessive tearing, conjunctivitis, and uncontrolled blinking (blepharospasm). The nose and mouth may perceive a stinging or burning sensation with excessive rhinorrhea or discharge of nasal mucous. Irritation of the respiratory tract may cause tightness of the chest, sneezing, and cough, as well as increased respiratory secretions. Severe lung injury and, consequently, respiratory and circulatory failure, characterize death in experimental animals after inhalation of CS. Irritation of the gastrointestinal tract may cause vomiting and/or diarrhea. When the skin is exposed, a burning sensation may be experienced, which may be followed by inflammation and redness. In hot and humid environments, the skin effects may be more severe and result in blistering. Some or all of these effects may occur, usually within 30 s of exposure, and disappear within minutes after the exposure. The irritation during exposure is so intensive that it causes the exposed individual to seek escape from the exposure. The lethal effect of CS in animals by inhalation is caused by lung damage leading to asphyxia and circulatory failure, or from bronchopneumonia secondary to respiratory tract injury. Furthermore, pathologic changes involving the liver and kidneys following exposure to high concentrations of CS are secondary to respiratory and circulatory failure. The reader is referred to numerous publications regarding the animal and human toxicity of CS.^{24,32-38}

Prior to testing in humans, chemicals and drugs must undergo extensive animal testing in multiple species and by many routes of administration, including the expected route of exposure. For CS, toxicity studies included eye and skin irritation, as well as incapacitating and lethality studies by aerosol or vapor exposure. The airborne dosage is expressed as Ct, which is the product of the concentration (C) in mg/m^3 multiplied by the exposure time (t) in minutes. The product is described as the inhalation exposure dosage in $\text{mg} \cdot \text{min}/\text{m}^3$. The terms LC_{50} and IC_{50} describe the airborne dosages lethal (L) or incapacitating (I) to 50% of the exposed population. Some of the animal studies on CS have been summarized by McNamara et al.³¹ CS aerosols were generated by various methods, and various species were exposed to a single exposure from 5 to 90 min. The toxic signs observed in mice, rats, guinea pigs, rabbits, dogs, and monkeys on acute exposure to CS were immediate and included hyperactivity followed by copious lacrimation and salivation within 30 s in all species except the rabbit. The initial level of heightened activity subsided, and by 5 to 15 min from start of the exposure, the animals exhibited lethargy and pulmonary stress, which continued for about 1 h on cessation of exposure. All other signs abated within 5 min on removal from the exposure atmosphere. Goats, pigs, and sheep did not exhibit hyperactivity on exposure. When toxic signs were noted, these occurred following exposure via all dispersion methods. Lethality estimates, expressed as LC_{50} , from acute exposures to CS dispersed from a 10% CS in methylene dichloride are as follows: rats, $1,004,000 \text{ mg} \cdot \text{min}/\text{m}^3$; mice, $627,000 \text{ mg} \cdot \text{min}/\text{m}^3$; and guinea pigs, $46,000 \text{ mg} \cdot \text{min}/\text{m}^3$. No deaths occurred in rabbits exposed to CS dosages of up to

47,000 mg · min/m³. CS at dosages of up to 30,000 mg · min/m³ did not kill any of the monkeys that had associated pulmonary dysfunction (i.e., pulmonary tularemia). The combined LCt₅₀ for CS dispersed from methylene dichloride for rats, mice, guinea pigs, and rabbits was calculated to be 1,230,000 mg · min/m³. The results from acute exposures to CS, sprayed as molten agent, were as follows:

Species	LCt ₅₀ (mg · min/m ³)
Rat	32,000
Mouse	42,000
Guinea pig	8,000
Rabbit	17,000
Dog	34,000
Monkey	50,000
LCt ₅₀ values have been rounded off.	

Because of their resistance to the lethal effects of CS, LCt₅₀ values could not be calculated for swine, sheep, and goats. However, the combined LCt₅₀ for mice, rats, guinea pigs, rabbits, dogs, monkeys, swine, sheep, and goats was estimated to be 300,000 mg · min/m³.

The results (LCt₅₀) from acute exposures to CS dispersed from M18 thermal grenades were as follows: rats, 164,000 mg · min/m³ and guinea pigs, 36,000 mg · min/m³. Results from acute exposure to CS dispersed from M7A3 thermal grenades are provided below.

Species	LCt ₅₀ (mg · min/m ³)
Rat	94,000
Guinea pig	66,000
Rabbit	38,000
Goat	48,000
Swine	17,000
Dog	30,000
Monkey	120,000
LCt ₅₀ values have been rounded off.	

When the results from all of the acute exposures are combined, the LCt₅₀ values are as follows: all non-rodents combined, 36,000 mg · min/m³; all rodents combined, 79,000 mg · min/m³; and all species combined, 61,000 mg · min/m³. The inhalation toxicity of CS₂, which is comprised of 95% CS, 5% Cal-o-Sil® , and 1% hexamethyldisilazane, has also been evaluated. The LCt₅₀ results from acute exposure to CS₂ are as follows: rats, 68,000 mg · min/m³; guinea pigs, 49,000 mg · min/m³; dogs, 70,000 mg · min/m³; and monkeys, 74,000 mg · min/m³.

Repeated-exposure studies on CS via the inhalation and oral routes have been conducted and the findings reported.³⁹ The inhalation studies conducted on rats and dogs are highlighted. In these studies, rats and dogs were exposed to thermally dispersed CS for 4 to 5 min per day, 5 days per week for 5 weeks. The total accumulated dosage (Ct) for dogs was $17,000 \text{ mg} \cdot \text{min}/\text{m}^3$ (daily Ct of $680 \text{ mg} \cdot \text{min}/\text{m}^3$), and for rats the dosage was $91,000 \text{ mg} \cdot \text{min}/\text{m}^3$ (daily Ct of $3640 \text{ mg} \cdot \text{min}/\text{m}^3$). During the exposure, rats manifested considerable hyperactive and aggressive behavior. In CS-exposed rats, accumulated dosages of 25,000 and 68,000 $\text{mg} \cdot \text{min}/\text{m}^3$ resulted in mortalities. No gross pathology was evident in any of the rats that died or the surviving animals that were sacrificed following completion of the exposures. Body weight losses in the CS-exposed animals were minimal, and no significant difference was noted in organ-to-body weight ratios following the 5-week exposure. Based on the findings, it was concluded that repeated exposure did not increase the susceptibility to the lethal effects of CS. Marrs and co-workers studied the effects of repeated inhalation doses (1 h/d, 5d/wk, for 120 days) of neat CS aerosol in rats, mice, and guinea pigs.⁴⁰ High concentrations of CS were fatal to the animals after only a few exposures. Mortality in the low- and mid-dose animals was not significantly different from controls. It was concluded that CS concentrations below $30 \text{ mg}/\text{m}^3$ were without deleterious effects. These concentrations are about 10 times the IC_{50} of an exposed human population in 1 min.

2. Ocular and Cutaneous Effects

The effects of CS on the rabbit eye have been examined after topical application of CS in methylene chloride.³² All animals manifested conjunctivitis, which had completely subsided within a few hours. Moderate injury involving the cornea was not observed. Application of more concentrated solutions of CS also had no effect on the cornea.

CS is a primary irritant that elicits injurious action on the skin when topically applied either as a powder or a solution or on exposure to CS aerosol. Excessive perspiration at areas of clothing contact may contribute to the development of dermal lesions. Gutentag et al. and Bowers et al. reported the occurrence of erythema and vesiculation in human subjects topically exposed to CS powder or CS solution.^{41,42} Skin exposure to CS aerosols at a concentration of $300 \text{ mg}/\text{m}^3$ for 45 min produced erythema and vesiculation, whereas skin lesions were not evident at an exposure duration of 30 min.⁴³ Workers in a CS manufacturing and processing plant developed rashes, pruritis, vesicles, and wheals, which may have been representative of sensitization and reaction to re-exposure. Rothberg⁴⁴ confirmed that both CS and CN could produce skin sensitization in guinea pigs when administered topically and intradermally.

3. Reproductive and Developmental Effects

The developmental toxicity of CS was studied by Upshall in rats and rabbits exposed via inhalation to test article at concentrations most likely to exist in riot-control

situations ($\sim 10 \text{ mg/m}^3$).⁴⁵ Fetuses were examined for abnormalities, and no significant increase in the numbers of abnormal fetuses or resorptions were noted. However, it should be noted that the exposure conditions (low dosages and short exposure duration [5 min]) may not have been adequate to assess the fetotoxic and teratogenic potential of CS. No data were given on maternal systemic toxicity or mortality. Teratology studies are routinely conducted at dosages that produce maternal toxicity. Based on the findings of the Upshall study, it is impossible to conclude definitively that CS would not be fetotoxic and/or teratogenic under other exposure conditions.

4. Genotoxicity and Carcinogenicity

The mutagenic potential of CS and CS2, a formulation containing CS in a mixture of 5% Cab-o-Sil® and 1% hexamethyl disilazane, have been studied in microbial and mammalian bioassays. CS was positive for mutagenicity in the Ames assay, as reported by von Daniken et al.,⁴⁶ however, subsequent findings by Zeiger et al.⁴⁷ indicated questionable genotoxicity for *S. typhimurium* and those of Reitveld⁴⁸ and Wild⁴⁹ non-mutagenic for *S. typhimurium*. CS2 was negative when tested in *S. typhimurium* strains TA98, TA 1535, and TA 1537 with or without metabolic activation.⁵⁰ The mutagenic potential of CS and CS2 was also assessed in mammalian genotoxicity assays, namely, the Chinese hamster ovary (CHO) assay for induction of sister chromatid exchange (SCE) and chromosomal aberration (CA), and the mouse lymphoma L5178Y assay for induction of trifluorothymidine (Tft) resistance.^{50–52} The results of the cytogenetic tests indicated that CS2 induced sister chromatid exchanges, chromosomal aberrations, and induction of Tft resistance.

CS2 was evaluated for carcinogenicity in 2-year rodent bioassays.⁵⁰ Compound-related non-neoplastic lesions of the respiratory tract were noted. Pathological changes observed in CS2-exposed rats included squamous metaplasia of the olfactory epithelium and hyperplasia and metaplasia of the respiratory epithelium; hyperplasia and squamous metaplasia of the respiratory epithelium were observed in mice exposed to CS2. Neoplastic effects were not observed in either rats or mice exposed to test article. Conclusions drawn from these findings suggest that CS2 is non-carcinogenic for rats and mice.

5. Metabolism, Metabolic Fate, and Mechanisms

CS is absorbed very rapidly from the respiratory tract, and the half-lives of CS and its principal bioconversion products are reported to be extremely short.⁵³ The disappearance of CS follows first-order kinetics over the dose range examined. CS spontaneously hydrolyzes to malononitrile,⁵⁴ and the latter is transformed to cyanide in animal tissues.^{55,56} Metabolically, CS undergoes conversion to 2-chlorobenzyl malononitrile (CSH_2), 2-chlorobenzaldehyde (oCB), 2-chlorohippuric acid, and thiocyanate.^{24,53,57–60} CS and its metabolites can be detected in the blood after inhalation exposure, but only after large inhalation doses. Following inhalation exposure of rodent and non-rodent species to CS aerosol, CS and two of its metabolites 2-chlorobenzaldehyde and 2-chlorobenzyl malononitrile were detected in the blood.^{53,59} Brewster and co-workers studied the fate of CS in rats following intravenous

and intragastric doses.⁶¹ Findings demonstrated that in most cases the majority of the administered dose was eliminated in the urine. *In vivo*, CS is converted to 2-chlorobenzaldehyde, which can undergo various metabolic pathways, namely oxidation to 2-chlorobenzoic acid with subsequent glycine conjugation or reduction to 2-chlorobenzyl alcohol with ultimate excretion as 2-chlorobenzyl acetyl cysteine or 1-O-(2-chlorobenzyl) glucuronic acid (refer to Figure 11.3). The principal urinary metabolites are 2-chlorohippuric acid, 1-O-(2-chlorobenzyl) glucuronic acid, 2-chlorobenzyl cysteine, and 2-chlorobenzoic acid.⁵⁸ Lesser amounts of 2-chlorophenyl acetyl glycine, 2-chlorobenzyl alcohol, and 2-chlorophenyl 2-cyano propionate were also identified. In the study by Leadbeater on the uptake of CS by the human respiratory tract, 2-chlorobenzyl malononitrile was detected in trace amounts in the blood;⁵³ however, CS and 2-chlorobenzaldehyde were not detected after exposure to a very high dose of CS ($C_t = 90 \text{ mg} \cdot \text{min}/\text{m}^3$). This finding is consistent with the CS uptake studies in animals and with the maximum tolerable concentration in humans, which is below $10 \text{ mg}/\text{m}^3$. It is unlikely that significant amounts of CS would be absorbed via inhalation at or near the tolerable concentration.

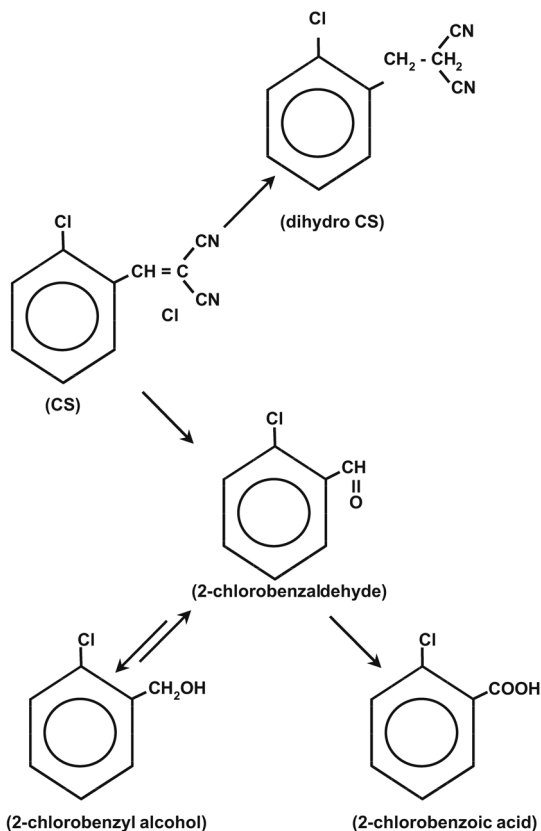


FIGURE 11.3 Principle metabolic pathways for CS.

The formation of cyanide from CS has been the subject of studies in laboratory animals and humans. Free cyanide has been detected following i.v. administration of CS in dogs exposed to lethal doses of CS, but little experimental data have been presented.⁵⁷ Studies by Frankenberg and Sorbo were conducted to determine thiocyanate excretion, blood cyanide levels, and the relationship between cyanide levels and symptomatology.⁶² They determined blood cyanide levels and thiocyanate excretion in mice following intraperitoneal dosing and inhalation exposure to CS. Mice were exposed to CS aerosol (20,000 mg · min/m³), corresponding to about 0.5 LD₅₀ of CS, and resulted in high levels of cyanide in blood that were reached quickly, with peak levels 4 to 16 min after injection. Equitoxic doses of malononitrile and cyanide were also evaluated for generating blood cyanide. It should be noted that CS and malononitrile possess two nitrile residues and may in theory give rise to two cyanide ions per molecule of the parent compound. This has been investigated and current evidence indicates that *in vivo*, only one cyanide radical is converted to cyanide; thus, the total amount of cyanide generated may be minimal.²⁴ Studies to ascertain cyanide production, measured as plasma thiocyanate levels, among human volunteers exposed to CS have been conducted.^{53,63} Negligible levels of plasma thiocyanate were detected in both studies.

Sulfhydryl-containing enzymes such as lactic dehydrogenase, glutamic dehydrogenase, and pyruvic decarboxylase are alkylated by CS.⁶⁴ CS also reacts with a number of nucleophilic moieties such as glutathione. Based on studies on the effect of CS on lactic dehydrogenase, Cucinell et al. postulated that the toxic effects of CS were the result of CS inhibition of sulfhydryl-containing enzymes.⁵⁷ For example, CS is known to react with the SH group of lipoic acid, a coenzyme in the pyruvate decarboxylase system. Regarding the mechanism of action of CS, it is theorized that the irritant and painful effect of CS may be due to bradykinin release.^{31,57} Ballantyne and Swanston have reported that both CS and CN are SN₂ alkylating agents, indicating that they react directly with nucleophilic sites.³⁸ Many of the toxic effects of these irritants may be due to alkylation of nucleophilic sites, including SH-containing enzymes.^{57,65} Interactions of electrophilic metabolites with nucleophilic moieties of biological material with potential consequences are highlighted in [Figure 11.4](#). The conversion of CS to cyanide with malononitrile as an intermediate has led Jones and Israel “To postulate that the toxic effects attributed to CS may arise from the conversion of CS *in vivo* to cyanide.”⁶⁶ Representative of detoxification is the NADPH-dependent reduction of the benzylidene double bond in CS to yield 2-chlorobenzaldehyde—a metabolic conversion that leads to a decrease in the lethal potency and peripheral sensory irritancy.

6. Human Toxicology

When exposed to CS, humans experience immediate signs and symptoms that disappear in minutes on cessation of exposure. CS causes only transient effects on the eye and irritation and blistering of the skin at high concentrations. Healthy individuals repeatedly exposed to CS do not manifest ill effects. Human volunteers have been exposed to CS under varying conditions and concentrations to determine the

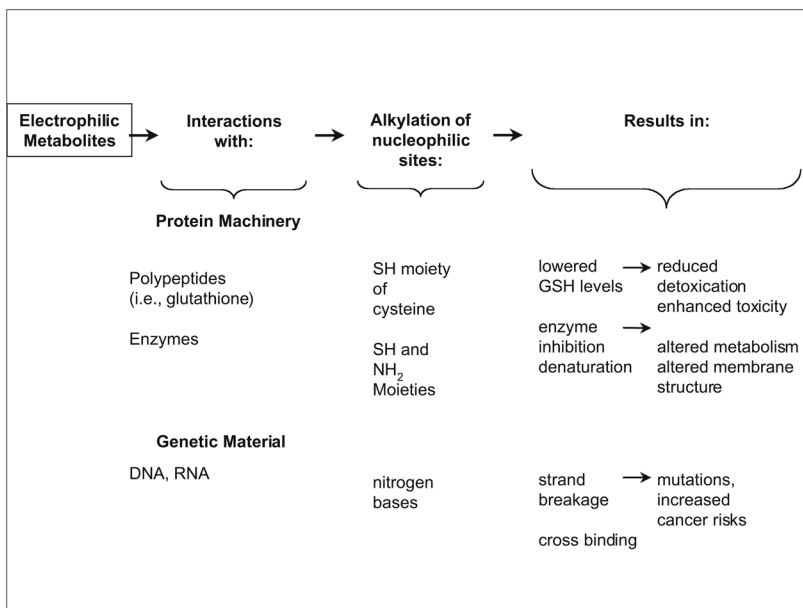


FIGURE 11.4 Interactions of electrophilic metabolites with nucleophilic moieties of biological material.

IC₅₀ value, defined as the concentration that will incapacitate 50% of the exposed population in one minute. The incapacitating signs and symptoms include intense burning of the eyes, nose, and respiratory tract; profuse lacrimation; excessive salivation; blepharospasm; tightness in the chest; and a feeling of suffocation.³¹ The time to incapacitation did not appear to differ among the test subjects exposed to CS via the different dispersion techniques, reduced ambient temperatures, or subjects with medical histories indicating respiratory, cardiovascular, or hepatic dysfunction.

However, at whole-body exposures at elevated temperatures (i.e., 95°F) and 35–97% relative humidity, the time to incapacitation was shortened. McNamara et al. reported that men may work without any signs of discomfort in an atmosphere where CS gradually accumulates, whereas these concentrations were intolerable to individuals entering the contaminated area from unexposed areas.³¹ Thus, it appears that adaptation develops gradually as the CS concentration increases. When the “tolerant” individual left the contaminated area for short periods of 10 to 30 min, the tolerance was lost, and re-entry into the contaminated areas resulted in intolerable irritation. Moreover, additional studies on human volunteers have documented the development of tolerance to CS.³⁴

Rose and Smith have reported alleged toxic reactions in human beings exposed to agent CS.²⁰ The Himsworth et al. report (Parts I and II) as to whether CS could produce serious toxic effects was the focus of an in-depth inquiry following the use of CS in Londonderry Northern Ireland in 1969.^{67,68} In their inquiry into the adverse

health and toxicological effects of CS, Himsworth et al. found no evidence, even among the most heavily exposed individuals of incapacitation that prevented their egress from a CS-contaminated environment. No evidence was found that previously healthy persons exposed 3 weeks before had developed any illness. Attention focused on susceptible subpopulations such as the elderly, the very young, pregnant women, and those with pre-existing cardiopulmonary dysfunction. Infants exposed to CS promptly recovered from the irritating effects of CS when removed to fresh air. There was no indication that CS exposure markedly altered the pre-existing pulmonary function of individuals with cardiopulmonary compromise. Pertaining to reproductive function and pregnancy, Himsworth et al. concluded that CS exposure had not significantly affected reproductive function.⁶⁸

Park and Giammona have described the effects of CS in a 4-month old infant following prolonged exposure.⁶⁹ The infant manifested severe respiratory distress and symptoms including copious nasal and oral secretions, sneezing and coughing, and upper airway obstruction. The patient was released from the hospital but was rehospitalized within 24 h with a diagnosis of pneumonitis. The patient was treated and released following a 28-day hospitalization.

Another report pertaining to the health effects of CS following its application in riot-control and law enforcement situations is that of Anderson et al.⁷⁰ They described the findings of a review of case studies of detainees presented for medical treatment following exposure to CS in a riot-control situation. The complaints were consistent with CS toxicity. During this civil disturbance, large quantities of CS were used in a confined area and under humid conditions. Two months after the incident, when the patients were asymptotic, the case notes of all patients who had presented to the clinic within 21 days after exposure with possible CS-related symptoms were reviewed. The most common complaint was coughing. Although the majority of patients had completely recovered within 2 weeks of exposure, one asthmatic child 10 years of age had sore throat and shortness of breath that persisted for 38 days following exposure. Additionally, a 3-month old infant with confirmed hematemesis was admitted to the hospital for observation. Since there was a 6 to 8 h delay from exposure to presentation at the clinic, the immediate and transient effects of lacrimation and rhinorrhea were not reported. There was a high incidence of skin burns, usually areas covered by clothing, and many of which healed with scarring and disfigurement. There was no clinical evidence of serious sequelae to CS exposure in the patients examined. However, the high incidence of burns due to the large amounts of CS generated in a confined area and a high humidity was a cause for concern. Anderson et al. confirmed the findings of Himsworth et al., at least with respect to the transient nature of riot-control agent-induced effects involving the eye and upper respiratory tract.^{67,68}

CS was adopted by the United States Army as its standard riot-control agent in 1959, and has largely replaced CN as the riot-control agent of choice worldwide. This was based on the low mammalian toxicity and the high sensory irritant potency of CS. It was used in the United Kingdom in 1969 to quell riots in Northern Ireland. In spite

of its extensive use, there have been no verified causes of death in humans following CS application.^{6,24,31} There have been several alleged reports of death following CS exposure; however, these were non-verifiable and/or incorrect. Hu reported that a middle-aged adult was overcome by CS and suffered heart failure and hepatic damage and eventually succumbed.¹⁰ A review of the original report of Krapf and Thalmann indicated that the subject did indeed suffer heart failure and hepatic insult.⁷¹ This individual was hospitalized, treated, and discharged 3 months after the exposure in a condition capable of work.

Additionally, a report focused on allegations that the Israeli Defense Forces had misused United-States-manufactured CS.⁷² The alleged misuse was reported to have caused numerous deaths, principally among the elderly and ill. The majority of casualties purported to be less than a year old or over 55 years of age. The Physicians for Human Rights reported in 1988 that they could not confirm that deaths were linked to tear gas exposure.⁷³ The United States Department of State did not have any medical evidence to support a direct causation between CS inhalation and the number of deaths reported. It was concluded that only four deaths might have been attributable to CS use by the Israeli Defense Forces. It also appears that at the time, Israel was utilizing two types of tear gas, but generally employed CN. Thus, the allegations of death following the use of CS in the West Bank and Gaza were unsubstantiated.

There are no authenticated reports of death from CS smokes.²⁴ Published estimates of the human acute lethal inhalation dosage of CS vary between 25,000 and 150,000 mg · min/m³. A widely quoted estimate of the human LCt₅₀ for CS, from United States sources, is 61,000 mg · min/m³. Estimates of lethal levels for man can be derived only by extrapolation from animal data since humans can withstand only minute dosages of riot-control agent. Also, in light of the array in lethal dose response noted in various animal species, conservative values should be adopted. Furthermore, estimates of lethal amounts on the basis of deaths occurring in law enforcement operations can be quite imprecise. The Himsworth et al. report (Part II) concluded that the physical properties of CS smoke and the unpleasant nature of the symptoms produced exposures that were self-limiting and short.⁶⁸ For irritants such as CS, a person is considered incapacitated when the exposed individual will no longer remain in the contaminated atmosphere. Motivated persons may remain in a cloud of irritant for longer periods of time, since a condition of adaptation occurs, and the irritant effects are diminished. The irritant ICT₅₀ for CS, which is considered intolerable for 1 minute is 0.1 to 10 mg/m³. However, the exact concentration depends on the individual's degree of motivation.³¹

B. DIBENZ (B,F)-1:4-OXAZEPINE (CR)

Dibenz (b,f)1:4-oxazepine (CR), a more recent addition to the riot-control family of compounds, was first synthesized in 1962. It is a potent sensory irritant of low toxicity. The overt signs (e.g., eye and skin irritation) of exposure are more transitory than those of other riot-control agents such as CS. CR does not induce vesication or contact sensitization.

1. Mammalian Toxicology

The low toxicity of CR has been demonstrated in various animal species following exposure via different routes—the data having been summarized by Ballantyne.⁷⁴ LD₅₀ and LCt₅₀ values for CR and the commonly used riot-control agents are summarized in Table 4. Comparison of the acute toxicity of CR to that of CN (1-chloroacetophenone) and CS (2-chlorobenzylidene malononitrile) indicates that CR is less toxic by all routes of exposure. CR-dosed animals exhibit ataxia (incoordination), spasms, convulsions, and rapid breathing. These effects gradually subside over a 15- to 60-min period, after which time the animals either appear normal, or there is increasing respiratory distress and death. Pathologic changes found in animals after i.v. and oral dosing included congestion of liver sinusoids and alveolar capillaries. Surviving animals manifest no gross abnormalities at necropsy and no histological abnormalities. After i.p. administration, toxic signs include muscle weakness and heightened sensitivity to handling. Toxic effects persist through the first day after exposure, and some animals exhibit CNS effects. Animals surviving the post-exposure period exhibit no gross or histologic abnormalities at necropsy. Ballantyne⁷⁴ also studied the effects of CR in various animal species following inhalation exposure. Animals were acutely exposed to varying exposure periods and test article concentrations of CR aerosol or CR smoke. Rats exposed to CR aerosol (13,050 to 428,400 mg · min/m³) manifested nasal secretions and blepharospasm (uncontrollable closure of the eyelids), which subsided within 1 h of cessation of exposure. There were no mortalities among the CR-exposed rats. In rabbits, guinea pigs, and mice exposed to CR aerosol, no deaths occurred at Ct of up to 68,400 mg · min/m³. Animals exposed to pyrotechnically generated CR manifested alveolar capillary congestion and intra-alveolar hemorrhage. Congestion of the liver and kidneys was also noted.

Pattle and co-workers⁷⁵ evaluated the potential of CR aerosol to produce physiological and ultrastructural changes of the lung. Rats were exposed to high dosages of CR aerosol (Ct = 115,000 mg · min/m³). Electron microscopy revealed that organelles (e.g., lamellated osmiophilic bodies) were not affected following exposure to CR. In studies by Colgrave et al., lungs were evaluated following exposure to CR aerosol at dosages of 78,200, 140,900, and 161,300 mg · min/m³.⁷⁶ The lungs appeared normal on gross examination; however, on microscopic examination, there were indications of mild congestion, hemorrhage, and emphysema. Electron microscopy revealed isolated swelling and thickening of the epithelium and early capillary damage, as evidenced by ballooning of the endothelium. The authors concluded that very high doses of CR aerosol produced only minimal pulmonary damage.

Lundy and McKay studied the effects of CR on the cardiovascular system.⁷⁷ These studies examined the effects of CR, administered via the i.v. route, on cardiovascular activity. A dose-dependent increase in blood pressure of short duration was observed. Stimulation of the heart rate and increased arterial catecholamine content were also noted following treatment with CR. The authors postulated that the CR-induced cardiovascular effect was related to sympathetic nervous system effects as evidenced by the abolition of CR-induced pressor effect by phentolamine and 6-hydroxydopamine.

Marrs and co-workers reported findings on the repeated-dose inhalation toxicity of aerosolized CR in mice and hamsters.⁷⁸ Animals were exposed to CR at test article concentrations of 204, 236, and 267 mg/m³ for 5 days per week for 18 weeks. Follow-up observations were conducted to detect recovery from or persistence of toxic effects. High concentrations of CR affected the survival of both species, and no single cause of death could be ascertained, although pneumonitis was evident in many cases. CR exposure produced minimal organ toxicity; however, chronic inflammation of the larynx was noted in mice. No significant pulmonary lesions were manifested; however, the occurrence of alveologenic carcinoma in a single low-dose group mouse and in a single high-dose group mouse was seen. The validity of these findings, as well as interpretations/conclusions, may be questioned since the spontaneous frequency of alveologenic carcinoma is high in many mouse strains.^{79,80} Further, this tumor type is dissimilar in many respects from human types of lung tumors. No lung tumors were noted in hamsters exposed to CR. Likewise, no lesions were present in the larynx of hamsters exposed to CR aerosol. Histopathologic evaluation of the liver revealed hepatic lesions in mice; however, these were of infective origin and not test article related. In general, Marrs et al. concluded that CR exposure at high concentrations reduced survivability and that CR produced minimal organ-specific toxicity at levels many times the intolerable human dose ($IC_{50} = 0.7 \text{ mg/m}^3$, within 1 min²⁴; $IC_{50} = 0.15 \text{ mg/m}^3$, within 1 min).^{78,81}

A number of studies have been reported on the repeated-dose toxicity of CR following dermal administration.^{82–84} Owens and co-workers studied the effects of CR following multiple dermal application in rabbits and monkeys.⁸² In the study by Marrs and co-workers, CR in acetone was applied to the skin of mice (5 days/wk for 12 wk).⁸⁴ The animals were kept for an additional 80 weeks following the end of the application period. No abnormalities were noted that could be attributed to CR, but a high incidence of fatty infiltration of the liver was noted in one strain of mice, which was most likely due to acetone. These investigators concluded that the repeated dermal application of CR had little effect on the skin. They further postulated that in view of the absence of any specific organ toxicity, absorption of even substantial amounts of CR would have little effect.

2. Ocular and Cutaneous Effects

CR was initially noted by Higginbottom and Suschitzky to cause intense lacrimation and skin irritation.⁸⁵ Studies on the irritancy of CR, CN, and CS in a number of species have been conducted.^{82,83,86–89} Owens et al. evaluated the ocular effects of 1% CR solutions in rabbits and monkeys following single- or multiple-dose application.⁸² Mild and transitory eye effects (mild redness, mild chemosis) were observed in rabbits and monkeys after a single dose of 1% CR solution. Multiple applications over a 5-day period of 1% CR solution to the eye produced only minimal ocular effects. Rengstorff et al. reported moderate conjunctivitis following the application of a 5% CR solution to the eyes of rabbits.⁸⁶ Histological examination revealed normal corneal and eyelid tissues. Biskup et al.⁸³ reported no signs of eye irritation in animals following single- or multiple-dose applications of 1% CR solution. Ballantyne and Swanston⁸⁸ also

studied the ocular irritancy of CR and arrived at a threshold concentration (TC_{50}) for blepharospasm in several species. Ballantyne et al.⁸⁹ conducted extensive studies on the ocular effects of CR as a solid (0.1 to 5 mg), as aerosol (360 to 571 mg/m^3 , 30 min exposure), and in solution (1 to 10% in polyethylene glycol). Measurements of intraocular tension and corneal thickness were conducted as well as histological examination of the eyes. CR in solution resulted in mild to moderate concentration-related ocular effects usually of several days duration—transient even at the higher concentrations. Solid CR resulted in lacrimation and minor irritation of the conjunctivae and eyelids. Exposure to CR aerosol ($Ct = 10,800 \text{ mg} \cdot \text{min}/m^3$; $Ct = 17,130 \text{ mg} \cdot \text{min}/m^3$) resulted in mild lacrimation and conjunctival injection with clearing in 1 h. CR solutions produced reversible dose-related increases in corneal thickness. Ballantyne et al. concluded that CR produced considerably less damage to the eye than CN and that there was a much greater degree of safety for CR than CN.⁸⁹

With regard to skin toxicity, CR produces a transient erythema; however, it does not induce vesication and contact sensitization or delay the healing of skin injuries.^{24,90} The burning sensation on exposure to CR persists for 15 to 30 min, and erythema may last for 1 to 2 h.

3. Reproductive Toxicity and Developmental Effects

The effects of CR on rabbit and rat embryonic development were studied by Upshall.⁹¹ Animals were exposed to aerosolized CR at concentrations of 2, 20, and 200 mg/m^3 for 5- to 7-min exposures. Additionally, some rats were dosed intragastrically at 2, 20, and 100 mg/kg on days 6, 8, 10, 12, and 14 of pregnancy, and others were dosed intragastrically with 400 mg/kg on days 7, 10, and 13 of pregnancy. Rabbits were dosed intragastrically with CR (0.2, 2, and 20 mg/kg) on days 6, 8, 10, 12, 14, 16, and 18 of pregnancy.

Recorded data included the number of litters, litter size and weight, number of abnormal litters, number of live fetuses, and placental weight. Pregnant female rats exposed to CR aerosol did not manifest toxic effects. There were no dose-related effects of CR on the parameters measured or the number or type of fetal malformations. Predominant abnormalities observed in all groups were skeletal in nature (e.g., poorly ossified sternebrae, extra ribs). Fetuses from female rats dosed intragastrically with CR exhibited skeletal anomalies in all groups. Pregnant rabbits exposed to CR aerosol did not manifest overt signs of toxicity. There were no dose-related effects of CR on any of the parameters measured and the numbers or types of malformation. No externally visible malformations were seen in any group. No dose-related effects of CR were noted in the fetuses in any group. Based on the overall observations, the authors concluded that CR was neither teratogenic nor embryotoxic to rats and rabbits.

4. Genotoxicity and Carcinogenicity

There is a paucity of data addressing the subject of genotoxicity with respect to CR exposure. A review of the database has identified a single study in the mainstream medical literature.⁹² In the above-cited study, the mutagenic potential of technical

grade CR and its precursor (2-aminodiphenyl ether) was evaluated. Various strains of *S. typhimurium* served as the microbial test for predicting mutagenic response. Mammalian assay systems for the detection of mutations consisted of the following: Chinese hamster cell mutagenesis (V79/HGPRT system); mouse lymphoma cell mutagenesis (L5178Y/TK+/TK-); and the micronucleus test (erythrocytes). CR and its precursor were negative in all assays. The results suggest that CR is not mutagenic; however, conclusions as to the genetic threat of CR to humans must await further genotoxicity testing utilizing additional genotoxicity assays. With regard to carcinogenicity, very little research has been conducted on the carcinogenic potential of CR or its ability to cause other chronic health effects.

5. Clinical Chemistry

Husain et al. studied the effects of CR and CN aerosols on clinical chemistry parameters (e.g., plasma glutamic-oxaloacetic transaminase (GOT), plasma glutamic-pyruvic transaminase (GPT), acid phosphatase, and alkaline phosphatase).⁹³ Rats were exposed via inhalation to aerosols of CR or CN. Animals exposed to CR aerosol exhibited no significant changes in plasma GOT and GPT activities or in acid and alkaline phosphatase activities. In contrast, CN-exposed animals manifested significant increases in GOT, GPT, acid phosphatase, and alkaline phosphatase activities. The conclusion drawn from the study was that exposure to CN aerosol could lead to tissue damage.

6. Metabolism, Metabolic Fate, and Mechanisms

The bioconversion and metabolic fate of CR has been studied in some detail.^{94–98} The subject of CR metabolism has been reviewed by Upshall.⁹⁹ Aerosols of CR are very quickly absorbed from the respiratory tract. Plasma half-life ($T_{1/2}$) of CR after inhalation exposure to CR aerosol is about 5 min. The plasma half-life of CR following i.v. administration is also about 5 min. Balfour studied the uptake and metabolic fate of CR in intact cornea and corneal homogenates.⁹⁴ The data indicated that these tissues readily took up CR and metabolized CR to a lactam derivative. The metabolism and fate of CR have been investigated in a series of *in vivo* and *in vitro* studies by French and co-workers and by Furnival et al.^{96–98} French et al. studied the *in vivo* metabolism and metabolic fate of CR in rats, guinea pigs, and monkeys after i.v. and intragastric dosing of CR.⁹⁶ In the rat, CR is converted to the lactam, followed by the subsequent hydroxylation to yield monohydroxylated derivatives (i.e., 4-, 7-, and 9-hydroxylactams) and the eventual formation of sulfate conjugates (see [Figure 11.5](#)). The pathway leading to sulfate conjugate formation of CR metabolites represents the major metabolic pathway in the rat irrespective of dose and the route of administration. The bile contained only small levels of sulfate conjugates. It should be noted that in his review on the metabolism of CR, Upshall discussed the formation of glucuronide conjugates of CR metabolic intermediates that are eventually excreted in the urine as sulfate conjugates.⁹⁹ French and co-workers also indicated that similar metabolic products and excretory pathways exist in the guinea pig and monkey; however, only free hydroxylactams were isolated from monkey urine.⁹⁶ In the same study,

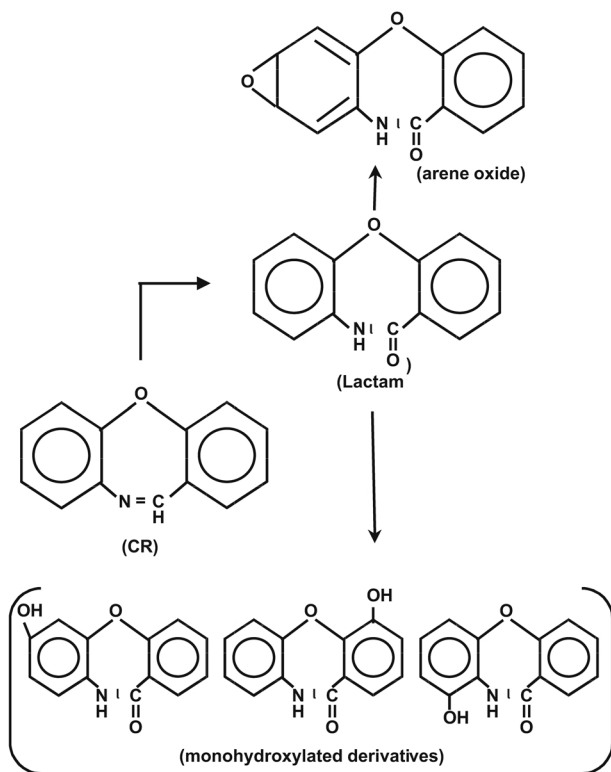


FIGURE 11.5 Bioconversion pathways for CR.

the authors reported the findings of whole-body autoradiography studies in CR-dosed mice, which demonstrated the rapid disappearance of CR from blood into other compartments (liver, kidney, and small intestine). These findings are consistent with the rat studies indicating the rapid absorption, hepatic metabolism, biliary secretion, enterohepatic recirculation, and renal excretion. Furnival et al., on the basis of *in vitro* metabolic studies using rat liver preparations, demonstrated that CR was metabolized via the following major pathways: (a) ring opening and reduction and (b) oxidation to lactams.⁹⁸ French et al. performed additional *in vitro* and *in vivo* metabolic studies.⁹⁷ Their findings supported 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.

7. Human Toxicology

The effects of CR on human subjects following aerosol exposures, “drenches” with dilute solutions, and local application have been reported by a number of investigators.^{37,88,90,100–105} The estimated human LCt_{50} of CR is over $100,000 \text{ mg} \cdot \text{min}/\text{m}^3$.

Human studies to determine the effects of CR after aerosol or cutaneous exposures were conducted, and the findings have been summarized in a National Academy of Sciences report.⁶ Human subjects manifested mostly ocular and respiratory effects after acute exposure to CR aerosol. Ocular effects consisted of lacrimation, irritation, and conjunctivitis; and respiratory effects included upper respiratory tract irritation, with choking and dyspnea. Ballantyne et al. described the effects of dilute CR solutions following “splash contamination” on the face.¹⁰¹ In addition to the classical effects on the eye, CR facial “drenches” also resulted in an immediate increase in blood pressure concomitant with decreases in heart rate. Subsequent studies were conducted by Ballantyne and co-workers on the effects of CR after whole-body “drenches.”³⁷ Immediate increases in blood pressure were noted, as in the previous study; however, Ballantyne et al. concluded that the cardiovascular effects described in both studies were not due to absorbed CR.³⁷ They theorized that there was insufficient CR uptake to cause the systemic effects on the heart, and the cardiovascular effects were due to the sensory-irritant-induced stress. However, Lundy and McKay suggested that the cardiovascular effects described by Ballantyne et al.¹⁰¹ were the result of CR-induced effects on the heart via the sympathetic nervous system.⁷⁷ Ashton et al. also studied the effects of CR aerosol on the respiratory physiology of humans.¹⁰² Test subjects were exposed to CR aerosol at a mean concentration of 0.25 mg/m^3 (particle size of 1–2 micron) for 1 h. Expiratory flow rate was decreased about 20 min after onset of exposure. The authors theorized that CR stimulated the pulmonary irritant receptors to produce bronchoconstriction and increasing pulmonary blood volume by augmenting sympathetic tone.

8. Ocular and Cutaneous Effects (Human)

Utilizing procedures developed for CS, Ballantyne and Swanston conducted a comparative study including human subjects to assess the irritant potency of CR.⁸⁸ Dilute solutions of CR (CR in saline) were applied to the eyes to ascertain the threshold concentration for producing blepharospasm (uncontrollable closure of the eyelids). The median threshold concentration (TC_{50}) to produce blepharospasm for man is $8.6 \times 10^{-7} \text{ M}$. Comparative TC_{50} values in several animal species are: $\text{TC}_{50} = 7.9 \times 10^{-5} \text{ M}$, rabbit and $\text{TC}_{50} = 3.5 \times 10^{-5}$, guinea pig. The TC_{50} to produce sensation on the human eye is $4.9 \times 10^{-7} \text{ M}$ ($9.1 \times 10^{-2} \text{ mg/l}$ solution). The authors suggested that CR at a concentration of $3.3 \times 10^{-6} \text{ M}$ would be incapacitating based on extrapolation from human eye data on sensation. In general, the data also indicate that the molar concentration required to elicit threshold effects on the human eye is smaller for CR than for CS. Ballantyne and Swanston also postulated that a CR concentration of less than 0.25 M (5% solution) would not produce structural damage to the eye when applied to the conjunctiva.⁸⁸ They also cited data by Hogg on the threshold irritant response (burning sensation) of the human eye to CR aerosol.¹⁰⁶ A TC_{50} for sensation of $4.0 \times 10^{-3} \text{ mg/m}^3$ ($4.0 \times 10^{-6} \text{ mg/l}$) was calculated for CR aerosol. Thus, the human eye is much more sensitive to CR aerosol ($\text{TC}_{50} = 4.0 \times 10^{-6} \text{ mg/l}$) than to CR in solution ($\text{TC}_{50} = 9.1 \times 10^{-2} \text{ mg/l}$). This is consistent with the report that the human eye is more sensitive to CS aerosol than to

CS in solution.⁸⁷ Other studies by these researchers included a study to ascertain the effect of CR solution (1% CR) splashed on the face and the effects of very dilute solutions (0.0025 to 0.001%) of CR on volunteer subjects exposed (whole body spray or showers) to test material.¹⁰¹ After a 15-s, individual drench with CR, subjects exhibited intense stinging of the eyes, injection of the conjunctivae, profuse lachrymation, and blepharospasm. The stinging of the eyes was rapid in onset, which occurred within seconds. Additionally noted was a very rapid onset of stinging of the skin around the eyes, which rapidly intensified to a strong, burning sensation. Group drenches of 1 min duration were also conducted. The ocular effects noted were similar to those observed in the individual 15-s drenches. Compared to CR, the effects elicited by CS were of shorter duration, less severe, and more variable. It should also be noted that following CS exposure, stinging of the eyes was the first biological effect seen. From the data, it was concluded that even very dilute solutions of CR (0.0025 to 0.001%) produced sensory ocular effects.

Over the years there has been considerable interest in the cutaneous effects of sensory irritant compounds, and several studies on the dermal effects of CR in humans have been published.^{90,100,101} Weigand and Mershon studied the dermal effects of dilute CR and CS solutions (CR in propylene glycol and CS in trioctyl phosphate).¹⁰⁰ Test subjects were patch tested on various anatomical sites with concentrations of test article ranging between 0.01 to 1.0%, and exposure duration was for 5 and 30 min. Stinging sensation was evident following exposure to both compounds, with CR eliciting a response of greater intensity. The onset of stinging was more prompt at higher ambient temperatures. Transient erythema of varying degrees was evident and subsided within 4 h.

Holland evaluated skin reactions to CR in humans following application of CR in graded quantities as CR powder or as dry material moistened with saline.⁹⁰ Erythema was noted in 10 min and faded on removal of test article. When moistened, CR resulted in marked irritation. No swelling or vesication was evident, even under adverse conditions. It was concluded that CR is capable of producing acute cutaneous discomfort. In comparing the results with similar studies on CS and CN, Holland concluded that all reactions to CR are mild and transient compared to that of CS, which resulted in an erythema of greater duration and to that of CN, which produced blistering.⁹⁰

Ballantyne and co-workers drenched volunteer subjects with very dilute solutions of CR and CS for 15- and 60-s durations.³⁷ In the studies comprising subjects that were exposed individually, stinging of the skin around the eyes was of rapid onset and spread to other parts of the face. The burning sensation involving facial skin was the next pronounced feature for about the first minute. Scalp and ears were not usually affected. During the second minute, stinging was associated with the back of the neck and irritation of the genital area. Stinging of the shoulder and back followed in 3 to 4 min, and the burning sensation was intense in approximately 5 min. After about 5 to 6 min, other anatomical sites (e.g., chest, abdomen, thighs, and buttocks) were affected. At 10 min, the burning sensation of the skin was intense, primarily affecting the trunk and back. Within 15 min, the skin sensation had subsided. By 20 min, skin sensations were reduced to mild tingling or had disappeared. Erythema of the skin was produced within several minutes and persisted for 1 to 2 h. No other skin changes

were noted. Many areas of the skin were somewhat resistant to irritation, which included such sites as the ears, nose, scalp, palms of the hands, knees, and the lower legs. In general, a more intense response was elicited by CR at higher concentrations; however, it should be noted that individual variations were more marked than the differences between CR concentrations. In the group drenching studies, burning of the skin was the most prominent symptom. As with the individual drenches, considerable variation in the severity of the symptoms was manifested. Compared with CR, the effects elicited by CS were less severe, of shorter duration, and more variable. Stinging of the skin followed a similar progression (face, neck, genital areas, shoulders and back, chest, abdomen, and thighs) as seen with the CR drenches. The studies by Ballantyne et al. demonstrated that very dilute solutions of CR and CS produce a strong stimulation of sensory receptors in the skin and mucous membranes.³⁷ The burning sensation was more intense and of longer duration on exposure to CR than with CS. Skin irritation and erythema were evident following exposure to either CR or CS, and the signs were more pronounced with CS than with CR. No individual drenched with CR or CS manifested edema, vesication, or desquamation.

C. CHLOROACETOPHENONE (CN)

Chloroacetophenone or CN, a white crystalline solid with an apple blossom odor, is commonly known as tear gas or Mace®. Chloroacetophenone was first synthesized in 1871 and was studied for its use as a tear gas shortly after World War I. CN acts directly on the mucous membranes to produce irritation, burning, and pain of the eyes, nose, throat, and respiratory tract. Ocular effects include lacrimation, blepharospasm, and conjunctivitis. Irritation of the respiratory tract produces sneezing, coughing, secretions, nasal congestion, and a sense of suffocation. The onset of some or all of these symptoms is immediate and persists from 5 to 20 min after removal from the contaminated atmosphere.

1. Mammalian Toxicology

Inhalation studies consisting of acute and repeated-dose have been conducted in various animals to ascertain the comparative toxicity of CN. The toxicology of CN has been reviewed and summarized in a National Academy of Sciences report, by McNamara et al., and by Hu.^{6,31,107} The early toxicity studies on CN were highly variable, and subsequent studies conducted in the mid-1960s using an array of animal species were designed to provide more quantitative data. In these studies, CN was dispersed in acetone or from commercially available thermal grenades. Sublethal effects observed on exposure to CN consisted of the following: lacrimation, conjunctivitis, copious nasal secretions, salivation, hyperactivity, dyspnea, and lethargy. Cutaneous effects seen in the exposed animals consisted mainly of erythema. Dyspnea was the salient biological finding on post-exposure, which was exhibited in all animals. Ocular (i.e., conjunctivitis) and dermal effects (i.e., erythema) persisted for 3 to 7 days after exposure. The primary cause of death following CN inhalation was from pulmonary damage. Lethality ($LC_{t_{50}}$) values for CN in various species are as follows: rat, $8,878 \text{ mg} \cdot \text{min}/\text{m}^3$; guinea pig, $7,984 \text{ mg} \cdot \text{min}/\text{m}^3$; and

dog, $7,033 \text{ mg} \cdot \text{min}/\text{m}^3$. Pathological findings in animals that died after CN aerosol exposures consisted of pulmonary congestion, edema, emphysema, tracheitis, bronchitis, and bronchopneumonia in dogs, and pulmonary congestion, edema, and bronchopneumonia in rats, mice, and guinea pigs. The pathological findings reported by Ballantyne and Swanston in animals that died after CN inhalation included congestion of the alveolar capillaries, alveolar hemorrhage, and excessive secretion in the bronchi and bronchioles.³⁸ There were also areas of acute inflammatory cell infiltration of the trachea, bronchi, and bronchioles.

McNamara et al. cited the findings of a repeated-dose study on the effects of thermally generated CN on guinea pigs, dogs, and monkeys.³¹ In one series of experiments, guinea pigs and monkeys were exposed on 10 consecutive days to CN at Ct from 2,300 to 4,000 $\text{mg} \cdot \text{min}/\text{m}^3$ for a total exposure dosage of 31,445 $\text{mg} \cdot \text{min}/\text{m}^3$. This dosage would be expected to be lethal to about 75% of the guinea pigs and 100% lethal to monkeys if given in a single exposure. This exposure regimen resulted in the death of five guinea pigs and no deaths in the exposed monkeys. The toxicity of CN is considerably less when administered in divided dosages. These findings were confirmed in further studies using dogs that were exposed on 10 consecutive days to Ct of CN ranging from 3,000–7,000 $\text{mg} \cdot \text{min}/\text{m}^3$ for a total dosage of 60,000 $\text{mg} \cdot \text{min}/\text{m}^3$. A subsequent repeated-dose study was also conducted in guinea pigs, dogs, and monkeys exposed daily for 10 days to Ct ranging from 4,200 to 13,000 $\text{mg} \cdot \text{min}/\text{m}^3$ for a total exposure of 88,000 $\text{mg} \cdot \text{min}/\text{m}^3$. This dosage was lethal in the majority of animals for all species tested. Overall, these studies demonstrated the lack of cumulative toxicity of CN when administered as repeat doses.

In a recent study, Kumar and co-workers reported findings on the effects of multiple exposure to CN and CR in mice.¹⁰⁸ Animals were exposed to test article at concentrations equivalent to the 0.05 LC_{50} (CN $87 \text{ mg}/\text{m}^3$ or CR $1008 \text{ mg}/\text{m}^3$) for 15 min/day for 5 and 10 days. Biochemical endpoints measured included blood glucose, plasma urea, transaminase enzymes (SGOT, SGPT), liver alkaline phosphatase (ALP), liver acid phosphatase (ACP), liver glutathione (GSH) levels, and hepatic lipid peroxidation (malondialdehyde [MDA] formation). Clinical parameters affected following repeated exposure included decreased hepatic glutathione and increased lipid peroxidation. The hepatic acid phosphatase increased after the 5-day exposure to CN 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, indicative of tissue injury. CR exposure did not produce significant alteration in hepatic biochemical parameters. Additionally, hyperglycemia was observed after exposure to CN, an effect previously reported by Husain.⁹³ It was suggested that the hyperglycemia was induced by 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. Overall, these findings were consistent with results reported by Ballantyne on the repeated-dose effects of orally administered CR in various animals.⁷⁴ Histopathologic changes following CN exposure included 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 centrilobular necrosis of hepatocytes following CN exposure. The National Research Council cited a sub-chronic study that was conducted under the National Toxicology Program.⁶ Mice and rats were exposed to CN aerosol for 13 weeks, and the findings indicated no gross clinical signs in rats or mice, except irritation of the eyes including opacity. No microscopic lesions were noted compared with controls.

2. Ocular and Cutaneous Effects

CN is a potent irritant and is more likely to cause serious eye effects than CS. The ocular irritation caused by CN signals avoidance and the intense lacrimation and blepharospasm initiates a defense mechanism. High concentrations of CN may result in chemical injury to the eye with corneal and conjunctival edema, corneal edema, erosion or ulceration, chemosis, and focal hemorrhages.^{109–111} CN-induced ocular effects on the rabbit eye following treatment with various CN formulations has been investigated by Ballantyne et al.⁸⁹ and Gaskins et al.¹¹² Ocular effects included lacrimation, chemosis, iritis, blepharitis, and keratitis; severity was dependent on the formulation.

Exposure to CN has been associated with primary irritation and allergic contact dermatitis.^{113–115} CN is a potent skin irritant and is more likely to cause serious effects to the skin than CS induces. Severe exposure to CN results in skin injury that may consist of severe generalized itching, a diffuse and intense erythema, severe edema, and vesication. In addition to being a more potent skin irritant than CS, CN is considered a more potent skin sensitizer.¹¹⁴

3. Genotoxicity and Carcinogenicity

Carcinogenicity bioassays have been conducted in rats and mice.¹¹⁶ There was no indication of carcinogenic activity of chloroacetophenone in male rats exposed to test article. Equivocal evidence of carcinogenicity of chloroacetophenone was based on findings in female rats, indicating an increase in fibroadenomas of the mammary gland. The findings of a 2-year inhalation bioassay in mice suggested no carcinogenic activity in male or female mice exposed to CN.

4. Metabolism, Metabolic Fate, and Mechanisms

Little is known about the metabolism and full metabolic fate of CN. Chloroacetophenone is converted to an electrophilic metabolite. It is a SN_2 alkylating agent that reacts with SH groups and other nucleophilic sites of biomolecules. Alkylation of SH-containing enzymes leads to enzyme inhibition with disruption of cellular processes. Based on the potential to disrupt enzyme function, Castro investigated the effects of alkylating agents, including CN, on human plasma cholinesterase.¹¹⁷ CN was found to inhibit ChE via a non-SH interaction. It is thought that some of the toxic effects of CN may be due to alkylation of SH-containing enzymes.

5. Human Toxicology

The initial LC_{50} estimate for humans, based on extrapolation from animal data, was $7,000 \text{ mg} \cdot \text{min}/\text{m}^3$, which was subsequently revised and established as $14,000 \text{ mg} \cdot \text{min}/\text{m}^3$. In human volunteer studies, the immediate effects on exposure to CN were a burning sensation or stinging in the eyes, nose, throat, and exposed skin. This was followed by lacrimation, salivation, rhinorrhea, and dyspnea. Lacrimation persisted for about 20 min post-exposure, while conjunctivitis and blepharospasm persisted for up to 24 h. High levels of CN may produce chemical injury to the eye characterized as corneal and conjunctival edema, chemosis, and loss of corneal epithelium.¹¹¹ Physical injuries may also occur following dispersion via grenade-type tear gas devices.^{109,111} Punte et al. studied the effects of CN on human subjects.¹¹⁸ Individuals were exposed to CN aerosol at a Ct below $350 \text{ mg} \cdot \text{min}/\text{m}^3$, which is considered the maximum safe inhaled dosage for humans. Common symptoms include rhinorrhea, lacrimation, blurred vision, conjunctivitis, and burning of the throat. Less frequent, but more severe symptoms included difficulty in breathing, nausea, and burning in the chest. Persistence of effects was negligible with no overt clinical signs noted approximately 10 min after cessation of exposure.

Varying values for the incapacitating dosage (IC_{50}) of CN have ranged from 20 to $50 \text{ mg} \cdot \text{min}/\text{m}^3$. The IC_{50} of CN is comparable to adamsite (DM), an early riot-control agent that replaced CN; however, it is considerably greater than the IC_{50} of CS, which replaced CN in turn. The estimate for the human LC_{50} of CN dispersed from solvent is $7,000 \text{ mg} \cdot \text{min}/\text{m}^3$ dispersed from grenades.³¹ Other reported estimates are in the range between 8,500 to $25,000 \text{ mg} \cdot \text{min}/\text{m}^3$. According to Punte et al.,¹¹⁸ the maximum safe inhaled dose of CN for man is estimated at $500 \text{ mg} \cdot \text{min}/\text{m}^3$. Pulmonary lesions may occur at the inhalation dosages, and the effects of CN exposure in confined spaces can be severe, as reported by Thornburn.¹¹⁹ Exposed individuals manifested lacrimation, conjunctivitis, conjunctival edema, upper respiratory tract irritation, cough, dyspnea, and skin burns. Death from high concentrations of CN may occur; the post-mortem examination may reveal edema and congestion of the lungs, alveolar hemorrhage, necrosis of the mucosal lining of the lungs, and bronchopneumonia.^{120,121} Lethal exposures to CN have been reported.^{119–121}

D. OLEORESIN CAPSICUM (OC)

Oleoresin capsicum (OC), an extract of pepper plants, is a mixture containing many substances and capsaicinoids, including the active ingredient capsaicin (8-methyl-N-vanillyl-6-nonenamide or [N-(4-hydroxy-3-methoxybenzyl)-8-methyl-trans-6-nonenamide]). OC is a highly effective irritant that has received much attention as a less-than-lethal agent in civilian, governmental, and military sectors, and OC spray (“pepper spray”) has gained popularity as a police weapon in recent years. Since OC is a natural product (capsicum fruits are established food additives), it is considered safe—a viewpoint that is not necessarily accurate. OC has been incorporated into a variety of formulations and marketed as “pepper gas,” “pepper mace,” and “pepper spray” for self-defense, criminal incapacitation, law-enforcement, and

riot-control purposes. Used as a spray, OC rapidly induces involuntary closure of the eyes and lacrimation. It also causes respiratory-related effects such as severe coughing and sneezing, nasal irritation, bronchoconstriction, and shortness of breath. OC also causes burning sensation of the skin and loss of motor control. Consequently, exposed individuals can in most instances be easily subdued. Acute effects of capsaicin and capsaicinoids are primarily associated with the respiratory system (e.g., bronchospasm, respiratory arrest, pulmonary edema) but may also include hypertensive crisis and hypothermia. There have been numerous reports concerning deaths related to OC use. Although a causal relationship has not been established, most of the reported deaths have occurred within 1 h following exposure. Literature can be obtained regarding the chemistry, physiology, and toxicology of OC, capsaicin, and capsaicinoids.^{122–130}

1. Mammalian Toxicology

Capsaicin, the active ingredient of *oleoresin capsicum* (OC), was prepared and evaluated for physiological effects in humans as early as the 1920s. Interest in the development of capsaicin as a riot-control agent decreased as research efforts were directed to the development of the newly synthesized agent, CS. Unlike other riot-control agents such as CS, CR, and CN, which have definite chemical compositions, *oleoresin capsicum* is a mixture of compounds containing capsaicinoids (capsaicin and structural analogs), various acids and esters, alcohols, aldehydes, ketones, and carotenoid pigments.^{131–134} Keller et al. have identified numerous compounds in OC by gas chromatography-mass spectrometry (GC-MS).¹³⁵ The capsaicinoid content of the dried fruit has been reported to range from 0.1 to 1%.¹²⁶ The capsaicinoid content of the *oleoresin* is as follows: capsaicin (~70%), dihydrocapsaicin (~20%), norhydrocapsaicin (~7%), homocapsaicin (~1%), and homodihydrocapsaicin (~1%). Capsaicin is considered to be the active ingredient of *oleoresin capsicum*, and little consideration has been given to the other capsaicinoids regarding biological effects and mechanisms. Generally, the capsaicin analogs have similar effects, although with different potencies.¹³⁴

Toxicological studies have been conducted on both OC and capsaicin; however, not much is known regarding the toxicity of OC. Because OC is a much-utilized food component, OC is widely regarded as safe, with a low-order of toxicity.¹³⁶ Data on the toxicology of OC is extant, particularly when administered by inhalation. However, recent inhalation studies on OC have indicated the low inhalation toxicity of OC.^{137,138}

The toxicology of capsaicin is much better characterized. Toxicological and pharmacological data on capsaicin have been derived from both animal and human studies to include inhalation exposures. The pharmacologic actions of capsaicin and capsaicinoids were characterized in the 1950s.^{139,140} More recent studies revisited the toxicology of these substances and LD₅₀ values (0.56 mg/kg, i.v.; 7.6 mg/kg, i.p.; 7.8 mg/kg, i.m.; 9.0 mg/kg, s.c.; 190 mg/kg, intragastric; 512 mg/kg, dermal; and 1.6 mg/kg, intratracheal) for capsaicinoids and capsicum extracts were reported by Glinsukon et al.¹⁴¹ It was reported by the same authors that the toxicity of capsaicin in the capsicum extract was about four-fold greater than that of pure capsaicin

administered intraperitoneally. Guinea pigs appear to be more susceptible than mice or rats, whereas hamster and rabbits are less vulnerable to the toxic actions of capsaicin. The probable cause of death is respiratory paralysis.

Capsaicin has profound, acute effects on respiratory function, and the pulmonary toxicology of capsaicin has been studied in some detail. Capsaicin may induce the Kratschmer reflex, which on inhalation of an irritant causes apnea, bradycardia, and a biphasic fall and rise in aortic blood pressure. Animals and humans exposed to capsaicin manifest bronchoconstriction, the release of the neuropeptide substance P from sensory nerve terminals, and airway mucosal edema.^{142–146} Capsaicin administration produces species-related pulmonary effects. In the guinea pig, intravenous and intra-arterial dosing induces bronchoconstriction.¹⁴⁷ In the dog and cat, i.v. administration of capsaicin results in bronchoconstriction that is dependent on a vagal cholinergic reflex. Aerosol exposure of cats to capsaicin also evokes a vagal-mediated cholinergic reflex bronchoconstriction.¹⁴⁸ A study designed to elucidate the mechanism by which capsaicin via aerosol exposure produces bronchoconstriction in guinea pigs suggests a vagal/cholinergic and non-cholinergic local axon reflex contributes to this effect.¹⁴⁹

The cardiorespiratory effects of capsaicin have been studied following i.v. administration, which resulted in a triphasic effect on blood pressure and altered cardiac parameters.^{150,151} Capsaicin induces complex effects on the cardiovascular system consisting of tachypnea, hypotension (seen in the Bezold-Jarish reflex), bradycardia, and apnea.

The neurotoxic action of capsaicin on C-fiber afferents is well-known, and capsaicin has been used as a selective probe to study the role of nociceptors and neurogenic inflammation.^{152–154} In animals, exposure to high doses of capsaicin and its analogs results in long-lasting insensitivity for stimuli such as pain, irritants, and temperature.¹²⁶ Capsaicin-induced desensitization may be manifested for weeks and associated with structural changes that are reversible. Long-term effects involving the respiratory tract are characterized by desensitization of the airways to chemical irritants and the marked inhibition of vagal bronchoconstriction effects.¹⁵⁵ Capsaicin-induced desensitization is caused by acute and excessive depletion of the neurotransmitter substance P, which is expressed as a lack of normal physiological response to stimuli such as heat and cold. High doses of systemic capsaicin induce a permanent or long-lasting desensitization of capsaicin-sensitive afferent nerves in newborn rats. In adult rats, the same doses provoke a long-lasting but temporary block of the nerves. In both cases, transmission of pain in response to various noxious stimuli was inhibited or abolished in capsaicin-treated animals. The effect is postulated to be capsaicin-induced with the consequent neurodegeneration of C-fiber receptors.¹⁴² More recently, reports suggested that this effect can be dissociated by using lower doses.¹⁵⁶

Alteration in thermoregulation can result on exposure to capsaicin and capsaicinoids. Weiss has reviewed some of the studies on capsaicin's effect on body temperature control and corroborated that capsaicin has been used for the last 25 years as the tool of choice in elucidation of physiological body temperature and pain control.¹⁵⁷ Pretreatment of rats and guinea pigs with capsaicin induced an irreversible

impairment in thermoregulation. On exposure to heat, body temperature rose concomitant with an inability to discriminate and seek cooler environments.¹⁵⁸ The capsaicin-treated animals consumed less water and became dehydrated. Dermal blood vessels failed to dilate, and the animals did not take appropriate behavior to prevent heat stroke. The same investigators reported that s.c. injections of capsaicin reduced body temperatures and that the dosing regimen resulted in a tolerance to thermal regulation. Frens reported that s.c. injections of capsaicin reduced body temperature in goats.¹⁵⁹ Topical treatment of human skin with 1% capsaicin and capsaicinoids lowered the threshold to thermal pain.¹⁶⁰ Weiss postulated that capsaicin and capsaicinoids might have potentially deleterious physiological consequences in individuals exposed to these substances at elevated temperatures, especially in repeated-exposure scenarios.¹⁵⁷

The effects of capsaicin and capsaicinoids on the gastrointestinal tract and nutritional impacts have been studied. The duodenal mucosal response to capsaicinoids and altered fat uptake by damaged duodenal epithelium, reported by Nopanitaya and Nopanitaya and Nye, led to further investigations concerning alteration of nutrient absorption and metabolism by capsaicinoids.^{161,162} Studies by Sambaiah et al.,¹⁶³ Sambaiah et al.,¹⁶⁴ and Kawada et al.¹⁶⁵ indicated that capsaicinoids had no adverse effect on fat intake or absorption. The lipotropic and hypolipidemic effects of capsaicinoids has been examined in some detail.¹⁶⁵⁻¹⁶⁷ It was postulated by Sambaiah and Satayanarayana that capsaicinoids counteract the accumulation of fat in the liver by the reduction of hepatic lipogenesis and/or increased oxidation of lipids in tissues.¹⁶⁸⁻¹⁷⁰ Repeated dosing of capsaicin and capsicum in the rabbit produced pathological changes in several organ systems.^{171,172} In the study reported by Lee, capsaicin resulted in hepatic necrosis following multiple-dose administration.¹⁷¹ Mice, fed a diet containing capsicum extract for 4 weeks, did not exhibit signs of toxicity.¹⁶⁹ Intragastric administration of capsaicin (50 mg/kg/day) or crude extract of capsicum (0.5 mg/kg/day) for 60 days was conducted in rats by Monsereenusorn.¹⁷⁰ The findings are in concordance with those reported by Nopanitaya.¹⁶⁸ Biochemical parameters affected by capsaicin and crude extract included significant reductions in plasma urea nitrogen, glucose, phospholipids, triglyceride, transaminase, and alkaline phosphatase.

2. Ocular and Cutaneous Effects

Typical ocular symptoms associated with exposure to OC aerosol exposure include lacrimation, conjunctival inflammation, redness, severe burning pain, swelling, and blepharospasm. The application of capsaicin to the eye causes neurogenic inflammation and unresponsiveness to chemical and mechanical stimuli. Topical application of capsaicin eliminates the blink reflex for up to 5 days following dosing.¹²⁵ Systemic administration of capsaicin is associated with trigeminal nerve fiber degeneration in the cornea.¹⁷³ In humans, exposure to OC can cause loss of the blink reflex.

Dermal exposure to aerosolized OC results in intense burning pain, tingling, edema, erythema, and occasionally blistering. Topical application of capsaicin has been reported to deplete the skin of substance P, somatostatin, prostaglandin, and acetylcholine.¹²⁵ Studies by Wallengren demonstrated that topical pre-treatment with

capsaicin enhances different experimental inflammations including allergic dermatitis.¹⁷⁴ Multiple exposures of the skin over a period of minutes exaggerate the response. It is postulated that capsaicin amplifies inflammation via the release of substance P from the skin.

3. Mutagenicity and Carcinogenicity

There is wide concern regarding the mutagenic and carcinogenic potential of capsaicinoids. The mutagenic potential of capsaicinoids has been evaluated in both microbial and mammalian mutation assays. The mutagenicity of capsaicinoids has been extensively tested in the Ames (*S. typhimurium*) assay.^{175–179} Buchanan and co-workers evaluated the mutagenicity of chili pepper oleoresins and capsaicinoids.¹⁷⁵ Neither the oleoresin nor the purified capsaicin produced mutations in *S. typhimurium*. Toth et al. reported that purified capsaicinoids exhibited mutagenic activity in the presence of liver-activating enzymes; however, the material was non-mutagenic when mouse liver fractions were used.¹⁷⁶ Damhoeri and co-workers studied the mutagenic potential of capsicum pepper (oleoresins) using *S. typhimurium* in the absence of metabolic activation.¹⁷⁷ Under the conditions of the assay, the oleoresins were found to be mutagenic. Nagabhushan and Bhide studied the mutagenicity of capsaicin in *S. typhimurium* strains with and without the S-9 liver fraction.¹⁷⁸ In mutagenicity studies by Gannett et al., capsicum and the ethanol extract of red pepper were evaluated using the TA 98 and TA 1535 strains of *S. typhimurium* in the absence and presence of metabolic activation.¹⁷⁹ Findings suggested that capsaicin and the pepper extract were not mutagenic. In the rec⁺/rec⁻ assay, capsaicinoids were non-mutagenic for *B. subtilis*.¹⁸⁰ A number of studies have also been conducted using mammalian cells (V79 cell line) to ascertain the mutagenic potential for capsaicinoids.^{178,179,181} In the V79 mammalian test system, Nagabhushan and Bhide reported that capsaicin was non-mutagenic.¹⁷⁸ However, studies by Gannett et al. and Lawson and Gannett using the V79 cell line suggested that capsaicin and capsaicinoids were genotoxic.^{179,181} Nagabhushan and Bhide studied the mutagenic potential of capsaicin using the Micronucleus Mutation Assay and found capsaicin positive for mutagenicity.¹⁷⁸ The mutagenic potential of capsaicin was assessed in the Dominant Lethal Assay by Narasimhamurthy and Narasimhamurthy and found not to be mutagenic.¹⁸² Overall, in spite of equivocal findings regarding the mutagenic potential, capsaicin and capsaicinoids should be regarded as genotoxic.

Capsaicin has been reported to induce mucous fibrosis in the oral cavity and may play a role in the development of esophageal cancer.^{183,184} When administered in the diet, capsaicin induced cancer in the mouse duodenum.¹⁷⁶ A rodent carcinogenesis bioassay to assess the carcinogenic potential of capsaicin was conducted by Toth and Gannett.¹⁸⁵ Increases were noted in the incidence of benign tumors (polyploid adenomas) in the cecum of treated animals. An increased rate of malignant tumors, however, was not evident. Chronic treatment with capsaicin appeared not to alter the general health of the animals, influence growth rate, or alter body weight. The effect of capsaicin on 12-O-tetradecanoylphorbol-13-acetate (TPA), widely used in tumor promotion studies, was examined by LaHann¹⁸⁶ and Sasajima et al.¹⁸⁷

LaHann¹⁸⁶ concluded that capsaicin appeared to facilitate the onset of TPA-induced tumorigenesis and that capsaicin might increase the risk of skin cancer. In the studies of Sasajima et al.,¹⁸⁷ capsaicin induced ornithine decarboxylase (ODC) activity, an enzyme used as an index of tumor promoting capability. There appears to be sufficient evidence that capsaicin may pose a tumorigenic threat.

4. Metabolism, Metabolic Fate, and Mechanisms

Capsaicin and capsaicinoids undergo bioconversion, which involves oxidative and non-oxidative pathways. The highest enzymatic activity is found in the liver, followed by extrahepatic tissues (e.g., kidney, lung, and small intestine). Saria et al. studied the distribution of capsaicin in tissues of rats following systemic administration.¹⁸⁸ Uptake in the CNS was rapid, and high levels of capsaicin were detected following i.v. dosing. Slow diffusion from the site of application was noted on s.c. administration; however, detectable levels of capsaicin were found in various tissues. Kawada and Iwai studied the *in vivo* and *in vitro* metabolism of the capsaicin analog, dihydrocapsaicin, in rats.¹⁸⁹ The parent compound was metabolized to metabolic products that were excreted in the urine mostly as glucuronides. The metabolic processes involved in the bioconversion of capsaicin and analogs were initially studied by Lee and Kumar.¹⁹⁰ They demonstrated the conversion to catechol metabolites via hydroxylation on the vanillyl ring moiety—findings later confirmed by Miller et al.¹⁹¹ The conversion of capsaicin by the liver mixed-function oxidase system to arene oxide is one example of metabolism to an electrophilic metabolite. Another pathway leading to highly reactive intermediates involves the formation of a phenoxy radical, which in turn may undergo subsequent conversion to a quinone type product.¹⁹² In addition to the above oxidative pathways, the alkyl side chain of capsaicin is also susceptible to enzymatic oxidation (oxidative deamination).¹⁹³ Capsaicin may also undergo non-oxidative metabolism via the hydrolysis of the acid-amide bond to yield vanillylamine and fatty acyl moieties^{189,194,195} (see Figure 11.6).

Presently, no definitive mechanism can solely account for capsaicin-mediated toxicity. A number of metabolic pathways are involved in the bioconversion to electrophilic metabolites (e.g., arene oxide, phenoxy radical, quinone). These moieties can interact with nucleophilic sites of macromolecules such as proteins, DNA, and RNA and are thought to be critical in the etiology of capsaicin-induced toxicity, mutagenicity, and carcinogenicity. The potential of covalent binding with microsomal protein, for example, may account for the impact of capsaicin on xenobiotic metabolizing enzymes and liver toxicity. Concerning mitochondrial energy metabolism, Yagi postulated that capsaicin and dihydrocapsaicin produce repression of NADH-quinone oxidoreductase activity, which confirms findings suggesting capsaicin induces inhibitory effects on hepatic mitochondrial bioenergetics.¹⁹⁶

5. Human Toxicology

Studies have been published concerning the human response to inhaled capsaicin.^{145,197–201} The human pharmacology of capsaicin has been reviewed by Fuller.¹²⁸ Watson et al. described the clinical effects in individuals exposed to oleoresin

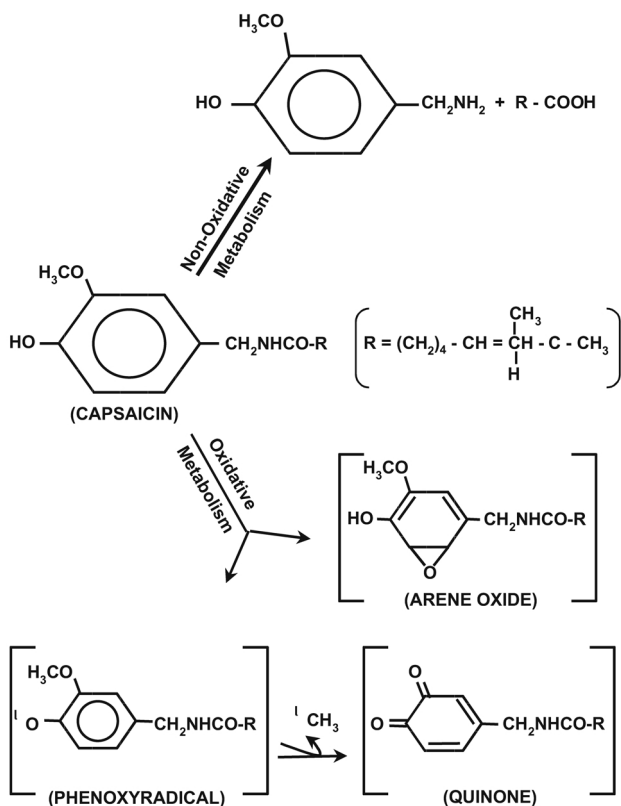


FIGURE 11.6 Bioconversion pathways for capsaicin.

capsicum.²⁰² The probable lethal oral dose of capsaicin for humans is considered to be 0.5 to 5.0 g/kg.²⁰³ The upper respiratory tract effects have been described.^{199,204} Healthy young human adult subjects who were challenged intra-nasally with capsaicin manifested rhinorrhea, sneezing, nasal burning, and congestion.¹⁹⁹ Capsaicin application to the nasal mucosa produced a painful sensation and copious secretion of nasal fluid, and these effects undergo desensitization after repeated application.²⁰⁴ Studies by Geppetti et al. support the hypothesis that the therapeutic effectiveness of capsaicin treatments in painful diseases might not be linked to nerve fiber degeneration due to the neurotoxic effect of capsaicin, but might rely on desensitization of the mechanism activated by capsaicin on the nerve terminal.²⁰⁴

The larynx may represent the primary site of stimulation of inhaled capsaicin.²⁰⁵ Bronchoconstriction has been the subject of a number of human studies on capsaicin.^{145,146,197} Fuller and co-workers demonstrated that when inhaled by humans, capsaicin caused a dose-dependent bronchoconstriction that was the same as in asthmatics and smokers.¹⁴⁵ The majority of subjects manifested coughing and all reported

retrosternal discomfort. The studies by Fuller and colleagues confirmed that the bronchoconstrictor reflex following capsaicin stimulation in animals is also present in humans.^{145,197} The capsaicin-induced bronchoconstriction and the release of substance P, a neuropeptide, are caused by stimulation of the C-fibers of the non-myelinated afferent fibers. These studies and those using isolated human airway preparations showed that repeated dosing causes tachyphylaxis. In humans, the mechanism of bronchoconstriction following inhalation of capsaicin is uncertain, but possible mechanisms can be inferred from animal studies. Capsaicin has been shown to release substance P, which can cause bronchoconstriction directly by activation of specific receptors or by release of histamine and other mediators. Capsaicin may also cause reflex bronchoconstriction by stimulating C fibers in both pulmonary and bronchial circulation. Therefore, bronchoconstriction could be secondary to substance P release or to a vagal reflex. In addition to the altered neurophysiology of sensory neurons in the airway mucosa, capsaicin also induces the release of tachykinins and neurokinin A. These biologically active substances in turn induce neuro-mediated inflammation of the epithelium, airway blood vessels, glands, and smooth muscle, which lead to bronchoconstriction, mucous secretion, enhanced vascular permeability, and neutrophil chemotaxis.^{206–208}

E. DIPHENYLAMINOCHLOROARSINE (ADAMSITE)

1. Toxicology and Physiological Effects

As previously stated, riot-control agents may be classified as to type (e.g., lacrimators, vomiting agents), based on a salient physiological effect. Diphenylaminochlorarsine (DM) is one of several compounds that include diphenylchloroarsine (DA), diphenylcyanoarsine (DC), and chloropicrin, which are classified militarily as vomiting agents. DM has been characterized as both a vomiting agent and sternutator and was known as adamsite during World War I. DM, which can cause great discomfort, has also been used as a riot-control agent, only by the United States according to Cookson and Nottingham.¹² DM is more toxic than other riot-control compounds—it is considered a potentially dangerous agent in view of a warning per Field Manual 3-10 that DM may not be used “. . . In any operation where deaths are not acceptable.” The estimated human LC_{50} is $11,000 \text{ mg} \cdot \text{min}/\text{m}^3$, as reported by Sidell.¹⁵ DM produces symptoms of slightly delayed onset and a relatively long recovery period. DM-related effects do not appear immediately as in the case of CN, CS, and CR. DM-induced effects occur in about 3 min after exposure begins and, depending on the severity of the exposure effects, may last for several hours.^{24,209} Unlike the other tear agents, DM is more likely to cause prolonged systemic effects. Signs and symptoms include eye irritation, upper respiratory tract irritation, uncontrolled sneezing and coughing, choking, headache, acute pain, tightness in the chest, nausea, and vomiting. Additionally, DM can cause unsteady gait, weakness in the limbs, and trembling. Ballantyne indicated mental depression as a prominent symptom following exposure to DM.²⁴ Exposure to high concentrations can result in serious illness as a result of pulmonary damage and edema or death.²⁰⁹

A number of investigations on the physiological effects of DM in various species of animals, including monkeys, have been conducted and are summarized in a National Academy of Sciences Report,⁶ by McNamara et al.³¹ and by Owens et al.²¹⁰ Following acute exposure to DM, animals exhibited ocular and nasal irritation, hyperactivity, salivation, labored breathing, ataxia, and convulsions. Punte et al. have reported the results of acute inhalation toxicity studies in several species following exposure (5 to 90 min) to high aerosol concentrations of irritant compounds which included DM.²¹¹ Toxic signs observed in animals were hyperactivity, ocular and nasal irritation, lacrimation, salivation, respiratory distress, and lethargy. Histopathologic examination revealed no abnormalities below an inhaled dose of $500 \text{ mg} \cdot \text{min}/\text{m}^3$ of DM. LC_{50} estimates were as follows: rat, $3,700 \text{ mg} \cdot \text{min}/\text{m}^3$; mouse, $22,400 \text{ mg} \cdot \text{min}/\text{m}^3$; and guinea pig, $7,900 \text{ mg} \cdot \text{min}/\text{m}^3$. The theoretical dose received can be calculated from the respiratory volume, the LC_{50} , and the estimated percent retention. The computed inhaled LD_{50} s for DM are as follows: rat, $14.1 \text{ mg}/\text{kg}$; mouse, $17.9 \text{ mg}/\text{kg}$; and guinea pig, $2.4 \text{ mg}/\text{kg}$. Animals exposed to DM at a dosage of $500 \text{ mg} \cdot \text{min}/\text{m}^3$ did not exhibit pathologic changes. Animals sacrificed or dying after exposure to DM manifested hyperemia of the trachea, pulmonary congestion and edema, and pneumonia. The clinical and pathologic findings parallel that observed on exposure to pulmonary irritants. Striker and co-workers studied the effects of DM in monkeys exposed to test article at varying concentrations and exposure periods ($855 \text{ mg}/\text{m}^3$ [3 min]; $1,708 \text{ mg}/\text{m}^3$ [5 min]; and $2,615 \text{ mg}/\text{m}^3$ [11 mins]).²¹² Toxic effects noted at the lowest exposure parameters were limited to a single animal exhibiting some oral and nasal discharge and with diminished response to stimuli. Exposure to a Ct of $8,540 \text{ mg} \cdot \text{min}/\text{m}^3$ resulted in ocular and nasal irritation, conjunctival congestion, facial erythema, and decreased responses—all signs abated within 24 h. Exposure to a Ct of $28,765 \text{ mg} \cdot \text{min}/\text{m}^3$ resulted in hyperactivity, copious nasal discharge, conjunctival congestion, marked respiratory distress, and gasping and gagging in all exposed monkeys. Eight deaths had occurred within 24 h in the high-exposure group. Necropsy of the high-dose group revealed congested and extremely edematous lungs. Microscopic examination revealed ulceration of the tracheobronchial tree and pulmonary edema. Additional studies in monkeys were also conducted by Striker et al.²¹³ The effects of “low” concentrations of DM were evaluated. Animals were exposed to DM at target concentrations of 100 and $300 \text{ mg}/\text{m}^3$ for exposure periods of 2 to 60 min and 2 to 40 min, respectively. A progression of toxic signs, characteristic of irritant gases, was noted as the exposure times were increased. At the maximum Ct of $13,200 \text{ mg} \cdot \text{min}/\text{m}^3$, animals exhibited nausea and vomiting, oral and nasal discharge, and conjunctival congestion. At Cts below $1,296 \text{ mg} \cdot \text{min}/\text{m}^3$, signs were restricted to blinking. Serious effects involving the eyes have been characterized as necrosis of the corneal epithelium on exposure to DM.³⁰

2. Human Toxicology

The human toxicology of DM has been reviewed by Ballantyne,²⁴ McNamara et al.,³¹ and Owens et al.²¹⁰ The earliest human study describing the effects following inhalation exposure to adamsite was that of Lawson and Temple.²¹⁴ Punter et al.¹¹⁸ and

Gongwer et al.²¹⁵ investigated the effects of varying concentrations of DM on human subjects. Punte and co-workers investigated the onset and persistency of effects following exposure to aerosolized DM and other irritant compounds in a small group of human subjects. The dosage had not exceeded $100 \text{ mg} \cdot \text{min}/\text{m}^3$, which was considered the maximum “safe” inhaled dose for man. Many of the experiments were terminated so as not to exceed the safe dosage. Subjects reported experiencing a burning sensation of the nose, throat, and chest, coughing and sneezing, and salivation. Several of the symptoms persisted for up to 2 h after termination of exposure. Based on their findings, the estimated ECt_{50} for irritation (3-min exposure) was $19 \text{ mg} \cdot \text{min}/\text{m}^3$. The dosage (Ct) required to elicit vomiting and nausea, however, could not be established. Additional human toxicological data were also examined by McNamara et al.³¹ McNamara cited a dosage of $49 \text{ mg} \cdot \text{min}/\text{m}^3$ necessary to cause vomiting and nausea, based on studies in humans exposed to DM at Ct between 7 and $236 \text{ mg} \cdot \text{min}/\text{m}^3$. However, high confidence in the above estimate is lacking since the estimate was founded on highly variable data. Ballantyne estimated a dosage of $370 \text{ mg} \cdot \text{min}/\text{m}^3$ was required to cause nausea and vomiting.²⁴ Inhalation of high concentrations of DM has resulted in severe pulmonary damage and death.²⁰⁹

VIII. SUMMARY

The desired effect of all riot-control agents is the temporary incapacitation of individuals via irritation of the mucous membranes and skin. Generally, riot-control agents can produce acute, site-specific toxicity where sensory irritation occurs (e.g., eyes, respiratory tract, and skin). The early riot-control compounds such as chloroacetophenone (CN) and chlorodihydrophenarsazine (DM) have been replaced with “safer” compounds such as CS and oleoresin of capsicum (OC). As much is known of the toxicity of riot-control agents such as chlorobenzylidene malononitrile (CS) as for many regulated chemicals such as pesticides. However, the widespread use of riot-control agents raises questions and concerns regarding their health effects and safety. For modern riot-control agents (e.g., CS and CR), there exists a large margin between dosages that produce harassment and dosages likely to cause adverse health effects. Yet, despite the low toxicity of modern riot-control agents, these compounds are not entirely without risk. The risk of toxicity increases with higher exposure doses and prolonged exposure durations. Pulmonary, dermal, and ocular damage may occur on exposure to high concentrations of these substances, particularly on exposure to DM or CN. Furthermore, it is best recognized that exposure to riot-control agents in enclosed spaces may produce significant toxic effects irrespective of the riot-control agent in question. Also, misuse of riot-control agents has resulted in varying degrees of eye and/or skin damage. Additionally, it is important to note that the intense physical discomfort and anxiety associated with riot-control chemicals may elicit cardiovascular changes that may have significant implications for individuals with pre-existing disease. Reported lethalties are few involving riot-control agents, and then only under conditions of prolonged exposure and high concentrations. Recently, concern has focused on the deaths resulting from law enforcement

use of OC, a riot-control agent generally regarded as safe since it is a natural product. As with other xenobiotics, not enough is known concerning the long-term/chronic effects of riot-control agents. Repeated-dose studies have been conducted for some of the riot-control agents; however, additional studies are needed to address concerns magnified by the potential of multiple exposures during situations of civil unrest. Clearly, there is considerable need for additional studies, both applied and basic, to define and delineate the biological and toxicological actions of riot-control agents.

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