REVIEW ARTICLE

Riot Control Agents: Pharmacology, Toxicology, Biochemistry and Chemistry[†]

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The desired effect of all riot control agents is the temporary disablement of individuals by way of intense irritation of the mucous membranes and skin. Generally, riot control agents can produce acute site-specific toxicity where sensory irritation occurs. Early riot control agents, namely, chloroacetophenone (CN) and chlorodihydrophenarsazine (DM), have been replaced with 'safer' agents such as *o*-chlorobenzylidene malononitrile (CS) and oleoresin of capsicum (OC). Riot control agents are safe when used as intended: however, the widespread use of riot control agents raises questions and concerns regarding their health effects and safety. A large margin exists between dosages that produce harassment and dosages likely to cause adverse health effects for modern riot control agents such as CS and dibenz[*b,f*]1:4-oxazepine (CR). 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 levels and prolonged exposure durations. Ocular, pulmonary and dermal injury may occur on exposure to high levels of these substances, and exposure to riot control agents in enclosed spaces may produce significant toxic effects. Reported deaths 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 because it is a natural product. As with other xenobiotics, not enough is known concerning the long-term/chronic effects of riot control agents. Clearly, there is considerable need for additional research to define and delineate the biological and toxicological actions of riot control agents and to illuminate the full health consequences of these compounds as riot control agents. Published in 2001 by John Wiley & Sons, Ltd.

INTRODUCTION

Riot control agents are highly potent sensory irritantsf relatively low toxicity that produce dose and time-dependent acute site-specific toxicity. Collectively, these compounds have been referred to as 'harassing agents' or as lacrimators, and in common parlance they are known as 'tear gases'. These chemicals interact pharmacologically with sensory nerve receptors associated with mucosal surfaces and the skin at the site of contamination, resulting in localized discomfort or pain with associated reflexes. This biological response, e.g. ocular irritation, results in pain in the eye (warning) and excess reflex lacrimation and blepharospasm (protection). The response is concentration-dependent and ceases on removal of the sensory irritant stimulus. Although intense lacrimation is a common reaction on exposure to riot control agents, it must be recognized that these compounds can elicit a diverse array of physiological effects. Thus, lacrimatory

compounds also may produce respiratory tract irritation and/or gastrointestinal irritation (i.e. nausea and vomiting). Riot control agents have both civil and military applications and have been classified as either military chemicals or chemical warfare agents. The common classification of military chemicals and chemical agents is based on a predominant physiological action, although classification also may be based on use, physical state or persistency.[1-4] Physiologically, riot control agents may be classified according to type: lacrimators, which primarily cause eye irritation and lacrimation; vomiting agents, which additionally cause vomiting; and sternutators, which mainly cause uncontrolled sneezing and coughing. Riot control agents also have 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. Thus, vomiting agents may be described erroneously as riot control agents and should be considered as a separate category of military chemicals—as they are in various military chemical classifications.[12] Moreover, it must be recognized that a 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 does not mean

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that it cannot be considered as a lacrimogenic compound. The classification issue may never be fully resolved, yet a system of classification serves to provide a basis for comparisons among chemical warfare agents and between chemical warfare agents and other chemicals. Verwey[13] has provided an excellent overview on the subject of classification; criteria to distinguish riot control agents from chemical warfare agents; and concepts pertaining to 'harassing', 'irritating' and 'incapacitating'. Characteristics common to riot control agents include: rapid onset of effect(s); relatively short duration of action following cessation of exposure; and relatively high safety margins. Ideally, in riot control situations these substances should produce 'harassing effects' that are relatively benign with a low incidence of casualties. Riot control agents should possess low acute toxicity and have toxicological and chemical properties that ensure minimal risks. The physicochemical and biological properties of the common riot control agents are highlighted in Table 1.

In the chemical warfare literature and in military Field and Technical Manuals, a distinction is made between military chemicals and chemical warfare agents. Of additional note is that the term 'military chemical compound' excludes chemical warfare agent. 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); incapacitating agents, i.e. adamsite (DM); lung irritants/choking agents, i.e. phosgene (CG); and blood agents, e.g. hydrogen cyanide (AC) and cyanogen chloride (CK). Military chemical compounds include the following categories: 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. Riot control agents are not considered by the USA as chemical weapons; however, some other countries do not draw a distinction. Military Field and Technical Manuals (i.e. Army FM 8-285) give definitions for chemical agent, military chemical and riot control agent.[20] Sidell[17] writing on the subject of riot control agents stated the following: "The United States does not recognize riot control agents as chemical warfare agents as defined in the Geneva Convention of 1925". Despite considerable attention and much 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.[11,21] Currently, the official policy on riot control agents by the USA is that riot control agents are not chemical warfare agents.[22]

HISTORICAL PERSPECTIVES

Lacrimatory and irritant compounds, many of which are listed in Table 2, have a history dating from World War I. They have been used in riot control and civil disturbances, military exercises and training and as chemical warfare agents. Chemicals used in World War I as tear gases

Table 1—Physicochemical and biological properties of common riot control agents

Compound	Physical properties[a]		Reactivity data		Rate of action	Biological values[b]		Lethal conc. (mg m^{-3})
	Physical state	Solubility	Stability	Hydrolysis rate		Threshold conc. (mg m^{-3})	Intolerable conc. (mg m^{-3})	
CN	Solid	Insoluble in water	Stable in closed containers	Slow	Instantaneous	1	5	850
CR	Solid	Limited solubility in water; readily soluble in organic solvents	Stable in storage	Very slow	Instantaneous	0.002	1	10,000
CS	Solid	Sparingly soluble in water; soluble inorganic solvents	Stable in storage	Slow	Instantaneous	0.004	3	2,500
DM	Solid	Insoluble in water; slightly soluble in common organic solvents	Stable in pure form	Very slow	Rapid	1	5	650
Capsaicin[c]	Solid	Sparingly soluble in water; soluble in inorganic solvents	Stable in storage	Slow	Rapid	—	—	—

[a] Physicochemical data: Refs 14–18 S. Katz, personal communication, 2000.
[b] Threshold values for eye irritation (CN,CR,CS) from Ref. 19; minimum lethal concentration for 10-min exposure.
[c] Capsaicin is the major ingredient of oleoresin capsicum (OC).

Table 2—Riot control and lacrimatory (tear gas) compounds

Compound	Chemical name	Code[a]	Application	
			Former	Current
Riot control				
CN	2-Chloroacetophenone	CN	War gas	Riot control
CR	Dibenz[*b,f*]1:4-oxazepine	CR	Riot control	Riot control
CS	σ-Chlorobenzylidene malononitrile	CS	Riot control	Riot control
Oleoresin of capsicum	OC, pepperspray[b]	—	Food additive	Food additive, incapacitant
Tear gases				
Acrolein	2-Propenal	papite	War gas	Intermediate[c]
Adamsite	10-Chloro-5,10-dihydro-phenarsazine	DM	War gas	Obsolete
Benzyl bromide	1-Bromotoluene	—	Intermediate	Intermediate[d]
Benzyl iodide	1-Iodotoluene	—	Experimental tear agent	Reagent
Bromoacetone	1-Bromo-2-propanone	BA	War gas	Reagent
Camite	α-Bromo-α-tolunitrile, bromobenzyl cyanide	CA,BBC	Riot control	Agricultural chemical
Chloroacetone	1-Chloro-2-propanone	A-stoff	War gas	Intermediate[c]
Chloropicrin	Trichloronitromethane	PS	War gas	Fumigant
Ethyl bromoacetate	Ethyl 2-bromoacetate	EBA	Riot control	Intermediate[e]
Ethyl iodoacetate	Iodoacetic acid, ethyl ester	KSK	Experimental tear gas	Reagent
Green Cross I	Phenylimidocarbonyl chloride	[f]	War gas	Reagent
Iodoacetone	1-Iodo-2-propanone	—	Experimental tear gas	Reagent
Tropilidene	1-Methoxy-1,3,5-cyclo-heptatriene	CHT	Tear gas	Tear gas
Xylyl bromide	α-Bromoxylene	T-stoff	War gas	Reagent

[a] Military code or identifier — usually one legitimate code designation.
[b] Active component = capsaicin (8-methyl-6-*trans*-nonenoyl-vanillylamide).
[c] Chemical intermediate for various industrial chemicals and pharmaceuticals.
[d] Chemical intermediate for certain industrial chemicals.
[e] Chemical intermediate for pharmaceuticals.
[f] Military designation = Green Cross I.

included acrolein (papite), bromoacetone (BA, B-stoff), bromobenzyl cyanide (CA,BBC), chloroacetone (A-stoff), xylyl bromide (T-stoff) and diphenylaminochloroarsine (DM). Chloropicrin (trichloronitromethane), a well-known chemical substance prior to World War I, was used both as a harassing agent and a lethal chemical during World War I. In fact, chloropicrin was one of a group of lethal agents, the others being chlorine, phosgene and trichlorethylchloroformate. Bromoacetone, a highly potent lacrimator, was the most widely used lacrimatory agent in World War I and xylyl bromide also was an early war gas.

Diphenylaminochloroarsine (adamsite), an arsenic-based compound having the military designation DM, was developed for use during World War I. Classified militarily as a vomiting agent and as a sternutator, DM was used as a riot control agent after the war. Chloroacetophenone was discovered over a century ago; however, it was not utilized in World War I. In contemporary terminology, it is referred to as 'mace' (Mace®)—a liquid mixture containing CN (active ingredient), hydrocarbons and freon propellant in 1,1,1-trichloroethane). It is of interest to note that prior to the development of chloroacetophenone the potent lacrimatory compound—ethyl bromoacetate—was the first riot control agent based on its use in Paris in 1912.[23] According to Royer and Gainet,[24] ethyl bromoacetate was

purported to have been used in the 1970s in riot control situations.

Military experience with harassing agents had prompted the utilization of these compounds in law enforcement operations; however, many of the military harassing agents were not suitable for law enforcement use due to concerns related to their likelihood to produce fatalities and/or total incapacitation. Thus, the development of modern riot control agents has been driven by requirements to develop safe and effective compounds that can be disseminated readily. Riot control agents are intended for temporary disablement—the intense irritant effects lead to a more-or-less pronounced incapacitation. The reader is referred to several sources that provide a more detailed discussion on the 'incapacitating' effects of riot control agents.[12,25–27] A systematic search of compounds suitable for temporary incapacitation and riot control was in place by the end of the World War I. Despite considerable research effects on a substantial number of candidate compounds, interest centered on CN and DM and subsequently CR and CS. Both CN and DM had become the harassing agents of choice, despite the early use of bromobenzyl cyanide (CA) as a riot control agent, and considerable stockpiles of CN and DM existed at the time of World War II. Although adamsite (DM) has been used as a riot

control agent, chloroacetophenone (CN) had become the lacrimator of choice by law enforcement personnel. Initially synthesized by Corson and Stoughton in the late 1920s,[28] chlorobenzylidene malononitrile (CS) was not developed as a riot control agent until the 1950s; CS has largely replaced CN for riot control use and is the most widely utilized tear gas (lacrimator) in riot control situations. Dibenz[b, f]1:4-oxazepine (CR), a riot control agent of recent origin, has seen limited application but this may, increase owing to the compound's greater potency and lower toxicity than some of the other riot control agents, including CS. The compound 1-methoxy-1,3,5-cycloheptatriene (CHT, tropilidene) has been demonstrated to be a potent irritant with physiological effects characteristic of riot control agents. Tropilidene toxicity is generally similar to that of CR. The naturally occurring substance oleoresin capsicum ('pepper spray'), a mixture with capsaicin as the major pungent component, may find increased utilization in law enforcement and riot control situations. '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.

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.
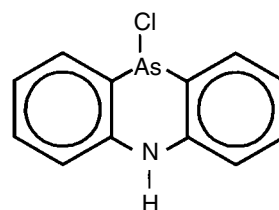
The structures of riot control agents CS, CR, CN, DM and capsaicin are depicted in Fig. 1. Table 1 highlights selected physical data on the common riot control agents. Table 3 summarizes physicochemical data of riot control agents, including adamsite and bromobenzylcyanide. In pure form, the common riot control agents are solids, although lacrimatory agents such as acrolein, chloroacetone and tropilidene 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 chemicophysical properties of the common riot control agents is presented.

Oleoresin capsicum (OC)

Oleoresin capsicum, a mixture of many compounds, is obtained by extracting dried, ripe fruit of chilli peppers, usually *Capsicum annuum* or *Capsicum frutescenes*. Its composition is variable and depends on factors such as maturity of the fruit, the environment in which the plants are grown and 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-6-*trans*-nonenoyl-vanillylamide) is the principal constituent. Capsaicin, particularly noted for its irritant properties, is the major pungent component in many peppers. Depending on the variety of chilli pepper, oleoresin capsicum contains 0.01–1.0% capsaicinoids on a dry mass basis. Some of the capsaicinoids (vanillylamides) found in oleoresin capsicum are capsaicin (~70%), dihydrocapsaicin (~20%), norhydrocapsaicin (~7%), homocapsaicin (~1%) and monodihydrocapsaicin

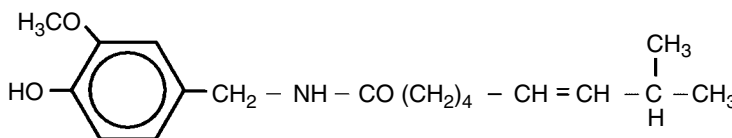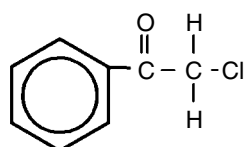2-Chlorobenzylidene malononitrile (CS)
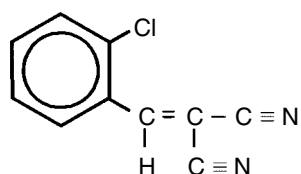
Dibenz[b, f]1:4-oxazepine (CR)

1-Chloroacetophenone (CN)

10-Chloro-5,10-diphenylarsazine (DM)
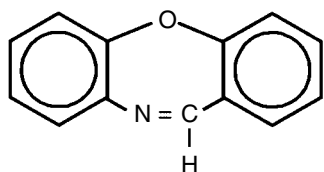
N-(4-Hydroxy-3-methoxybenzyl)-8-methyl-6-nonenamide (capsaicin)

Figure 1. Structures of CN, CR, CS, OM and capsaicin.

Table 3—Riot control agents: comparative physicochemical data[14–17]

Compound	CS	CR	CN	Capsaicin[a]	DM	CA
Molecular wt	188	195	154	305	277	196
Melting point	93 °C	72 °C	54 °C	64 °C	195 °C	25 °C
Vapor pressure at 20 °C (mm Hg)	0.00034	0.00059	0.0054	—	2×10^{-13}	0.011
Volatility (mg/m^3 per °C or mg/m^3/°C)	0.71/25	0.63/25	34/20	—	—	271/30
Solubility[b]	IOC	IOC	IOC	IOC	O	IO
Persistence	Varies	Persistent	Short	Fairly persistent	Persistent	—
Odor	Pepper-like	Odorless	Apple blossoms	Odorless	Bitter almond	Decaying fruit

[a] Capsaicin is the major pungent component of oleoresin capsicum (OC, pepper spray).
[b] Solubility: I = limited in water; O = soluble in organics; C = soluble in chlorinated organics.

(∼1%). Other components (e.g. phenolic compounds, acids and esters) of oleoresin capsicum also may possess irritant properties.

Chlorobenzylidene malononitrile (CS)

Chlorobenzylidene malononitrile is a variant of the riot control agent bromobenzylcyanide (CA), which dates from about 1920. Chemically, CS is 2-chlorophenyl-methylenepropanedinitrile or β, β-dicyano-o-chlorostyrene. Of note is that riot control agent CS exists as a family of three forms: CS, CS1 and CS2. The agent symbol 'CS' identifies the compound in pure form and the symbols 'CS1' and 'CS2' identify mixtures of crystalline agent and an aerogel. CS is prepared as the condensation product of o-chlorobenzaldehyde and malononitrile or the condensation product of o-chlorobenzaldehyde with cyanoacetamide and subsequent dehydration. It is a white crystalline powder with a molecular weight of 188 corresponding to a molecular formula of $C_{10}H_5N_2Cl$. The melting and boiling points are 93 °C and 310 °C, respectively. It has a pungent pepper-like odor and is immediately detectable. The vapor is several times heavier than air, and the vapor pressure of the solid is 0.00034 mmHg at 20 °C. It is sparingly soluble in water and readily soluble in methylene chloride. The molar solubility in water at 20 °C is 2.0×10^{-4} mol l^{-1} (= ∼4 mg 100 ml^{-1}) and CS hydolyzes somewhat slowly—the hydrolysis products are o-chlorobenzaldehyde and malononitrile. Chemically, CS is the most persistent of lacrimatory agents and will absorb into most porous surfaces.

Dibenz[b,f]1:4-oxazepine (CR)

Dibenz[b, f]1:4-oxazepine, having the military designation CR, is synthesized by the reaction of o-acylamino-diphenyl ether and polyphosphoric acid and other methods can be used to obtain the product. It is a pale yellow solid that is chemically stable in organic solvents. It has a molecular weight of 195 corresponding to a molecular formula of $C_{13}H_9ON$. The molar solubility in water at 20 °C is 3.5×10^{-4} mol l^{-1} (= ∼7 mg 100 ml^{-1}). The melting and boiling points are 72 °C and 335 °C, respectively. The vapor is 6.7 times heavier than air. The vapor pressure of the solid is 0.00059 mmHg at 20 °C. It is soluble in water and in organic solvents (e.g. ethanol, propylene glycol). Riot control agent CR solution consists of 0.1% CR dissolved in a solution of 80 parts of propylene glycol and 20 parts of water. It may persist for prolonged periods in the environment because, as a class of compounds, benzodiazepines are very stable in aqueous media.

Chloroacetophenone (CN)

Chloroacetophenone was specifically developed as a riot control agent and is referred to also as ω-chloroacetophenone, α-chloroacetophenone, phenacyl chloride, 2-chloro-l-phenylethanone and phenyl chloromethyl ketone. It is prepared by the chlorination of acetophenone with selenium oxychloride and has the military designation CN. This lacrimator was developed shortly after World War I and was used extensively as a training agent. Both CN and its variants (e.g. CNB CNC and CNS) replaced DM- and D-series riot control agents. At present, CN is considered obsolete by the US military; however, it is still common in police agency mixtures. It survives as the principal component in a liquid mixture under the tradename 'Mace'. It is a crystalline solid having a molecular weight of 154.5 corresponding to a molecular formula of C_8H_7OCl. The molar solubility at 20 °C is 4.4×10^{-3} mol l^{-1} (= 68 mg 100 ml^{-1}). Melting and boiling points are 54 °C and 247 °C, respectively. The density of the solid is 1.31 g cm^{-3} at 0 °C and the density of the liquid is 1.187 g m^{-3} 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.

Adamsite (DM)

Diphenylaminochloroarsine was developed as a chemical variant of diphenylchloroarsine and is commonly known as adamsite, with the military designation DM. It was produced worldwide until it was superseded by the CN-series of lacrimatory compounds. In the past, DM has found use also as an effective pesticide. It has a molecular weight of 277 with a molecular formula of $C_6H_4(AsCl)(NH)C_6H_4$. It 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} mmHg 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 it is in the form of an aerosol. Hydrolysis products are hydrochloric acid and diphenylarsenious acid. The nausea-causing effect and toxic by-products (i.e. arsine-based compounds) has led to its discontinued use/ban on civilian populations.

ACUTE SENSORY IRRITATION OF RIOT CONTROL AGENTS

Ocular Effects

Many chemicals possess more or less lacrimatory properties, varying in irritancy from mild to very severe. Irritancy data (ocular) and human toxicity estimates for the common riot control agents are highlighted in Table 1, and the comparative ocular irritancy for humans of various lacrimatory compounds is presented in Table 4. The most characteristic property of riot control agents is their ability to cause an intense and immediate stinging sensation in the eyes, with tearing at low concentrations, resulting in a temporary disabling. Low levels of riot control agents produce reversible and non-injurious effects; however, with some of these compounds high concentrations can produce ocular injury. Excessive exposure to riot control agents can produce ocular injury such as corneal edema, which is reversible. More serious consequences involving the eye following exposure to riot control agents include corneal ulceration and scaring, corneal opacification and corneal vascularization. Tearing agents that have been associated with ocular injury include chloroacetophenone (CN), chloracetone and bromobenzyl cyanide. Concerning ocular injury and desemination techniques, it may be stated that ocular injuries are more prevalent following use of explosive (thermal type) tear gas devices as contrasted to solvent spray-type tear gas devices. MacLeod[30] has provided a description of the differences between thermal and solvent spray devices. The reader is referred to a number of publications (which include reviews) regarding riot control agent-induced ocular injury.[30-39] Ocular effects are described in greater detail for each of the main riot control agents.

Oleoresin capsicum (OC), capsaicin and capsaicinoids.

Typical ocular signs and symptoms associated with exposure to aerosols of oleoresin capsicum consist of lacrimation, conjunctival inflammation, redness, severe burning pain, swelling and blepharospasm. In humans, exposure to OC can cause loss of the blink reflex. Capsaicin applied to the eye leads to neurogenic inflammation (vasodilatation and extravasation) and unresponsiveness to chemical and mechanical stimuli. It has been reported that the topical application of capsaicin eliminates the blink reflex for up to 5 days following dosing.[40] Systemic administration of capsaicin is associated with trigeminal nerve fiber degeneration in the cornea.[41]

Chlorobenzylidene malononitrile (CS).

The ocular effects of CS (aqueous and non-aqueous solutions) have been studied in both animals and humans.[42-49] The effects on the rabbit eye have been examined following topical application of CS.[42] Conjunctivitis was a common finding, 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. Animal studies have demonstrated that the potential for eye damage with CS is significantly less than with CN.[47,49] Studies by Ballantyne and Swanston[48] indicate that the human eye is more sensitive to CS aerosol than to CS in solution.

Dibenz[b,f]1:4-oxazepine.

Higginbottom and Suschitzky[50] had reported the occurrence of intense lacrimation and skin irritation on exposure to CR. Studies on the irritancy of CR and that of the riot control agents CN and CS have been conducted in various animal species.[48,51-55] Owens et al.[51] evaluated the ocular effects of 1% CR solutions in rabbits and monkeys after single- or multiple-dose application. Mild and transitory eye effects, namely, slight redness and mild chemosis, were observed in rabbits and monkeys after a single application of 1% CR solution. Multiple applications over a 5-day period of CR solution to the eye resulted in only minimal ocular effects. Rengstorff et al.[55] reported moderate conjunctivitis following the application of CR (5% solution) to the eyes of rabbits, and histological examination revealed normal corneal and eyelid tissues. Biskup et al.[54] also reported the absence of ocular irritation in animals following single- or repeated-dose applications of 1% CR solution. The ocular irritant potential of CR in several species was studied also by Ballantyne and Swanston[52] who formulated estimates of the median threshold concentration (TC_{50}) for blepharospasm. By utilizing procedures developed for CS, they conducted a comparative study including human subjects to assess the irritant potency of CR. Dilute solutions of CR in saline were applied to the eyes to ascertain the threshold concentration for producing uncontrollable closure of the eyelids (blepharospasm). Comparative TC_{50} values computed for several animal

Table 4—Ocular irritancy thresholds and toxicity estimates for human responses to various lacrimogenic compounds[1,2,4,6,10,12,17,19,29]

Compound	Ocular irritancy	Rate of action	Irritancy[a] threshold (mg m^{-3})	Intolerable[a] conc. (mg m^{-3})	Lethal[b] conc. (mg m^{-3})
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
DM	High	Rapid	~1	5	650
Xylyl bromide	High	Rapid	~5	15	5600

[a] When more than one value has been reported, a range is given.
[b] Estimate for minimal lethal concentration for 10-min exposure.

species are: $TC_{50} = 7.9 \times 10^{-5}$ M for rabbit; $TC_{50} = 3.5 \times 10^{-5}$ for guinea pig. The TC_{50} to produce sensation on the human eye is 4.9×10^{-7} M (9.1×10^{-2} mg l^{-1} solution). It was determined that the TC_{50} to produce blepharospasm for man is 8.6×10^{-7} M. It was suggested that CR at a concentration of 3.3×10^{-6} M would be incapacitating, based on extrapolation from human eye data on sensation.[52] In general, their findings suggest that the molar concentration required to elicit threshold effects on the human eye is less for CR than for CS. They further postulated that a CR concentration of < 0.25 M (5% solution) would not produce structural damage to the eye when applied to the conjunctiva. Ballantyne and Swanston also cited data by Hogg[56] on the threshold irritant response (burning sensation) of the human eye to CR aerosol. A TC_{50} for burning sensation of 4.0×10^{-3} mg m^{-3} (4.0×10^{-6} mg l^{-1}) was calculated for CR aerosol. Thus, the human eye is much more sensitive to CR aerosol ($TC_{50} = 4.0 \times 10^{-6}$ mg l^{-1}) than to CR in solution ($TC_{50} = 9.1 \times 10^{-2}$ mg l^{-1}). Other studies reported by Ballantyne et al.[57] included an investigation to ascertain the effect of CR solution (1% CR) splashed on the face, and a study on the effects of very dilute solutions (0.0025–0.001%) of CR on volunteer subjects subjected to whole-body exposures. After a 15-s individual drench with CR, subjects experienced intense stinging of the eyes, profuse lachrimation, injection of the conjunctivae and blepharospasm. The stinging of the eyes was very rapid in onset, occurring within seconds. Additionally there was a rapid onset of stinging of the skin around the eyes, which rapidly intensified to a strong burning sensation. Group drenches of 1 min in duration also were conducted. The ocular effects noted were similar to those observed in the individual 15-s drenches. Compared with CR, responses elicited by CS were of shorter duration, less severe and more variable. It should be noted also 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 (0.0025–0.001%) produced sensory ocular effects. Ballantyne et al.[53] also conducted extensive studies on the ocular effects of CR as an aerosol (360–571 mg m^{-3}, 30-min exposure), as a solid (0.1–5 mg) and as a solution (1–10% in polyethylene glycol). Measurements of intraocular tension and corneal thickness were conducted, as well as histological examination of the eyes. The CR in solution resulted in mild to moderate concentration-related ocular effects that persisted for several days–transient at the higher concentrations. Solid CR resulted in lacrimation and minor irritation of the conjunctivae and eyelids. Exposure to CR aerosol (Ct of 10 800 and 17 130 mg·min m^{-3}) resulted in mild lacrimation and conjunctival injection, with clearing in 1 h. Solutions of CR produced reversible dose-related increases in corneal thickness. Ballantyne et al.[53] 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.

Chloroacetophenone (CN). Chloroacetophenone is a highly potent irritant that is more likely to cause serious eye effects than either CR or CS. The ocular irritation caused by CN signals avoidance, and the intense lacrimation and blepharospasm initiate 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.[34,58,59] The CN-induced ocular effects on the rabbit eye following treatment with various CN formulations have been investigated by Gaskins et al.[47] and Ballantyne et al.[53] Ocular effects included lacrimation, chemosis, iritis, blepharitis and keratitis, the severity depending on the formulation of CN.

Adamsite (DM). Immediate effects such as eye irritation and lacrimation on exposure to DM are similar to those associated with tear gas compounds.[6,60] Local application of DM to rabbit eyes resulted in conjunctivitis, blepharitis and corneal opacity.[61] Ballantyne[29] described the ocular effects of human inhalation exposure to DM, consisting of lacrimation, blepharospasm and eye pain. Additionally, DM has been noted to produce necrosis of the corneal epithelium in humans.[62]

Dermal effects

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

Capsaicin/capsaicinoids. Dermal exposure to aerosolized OC produces an intense burning pain, tingling, edema, erythema and occasionally blistering. Carpenter and Lynn[63] studied the dermal sensory and vascular response in humans following topical application of capsaicin. Topical application of capsaicin has been reported to deplete the skin of a variety of biochemical constituents, including substance P, somatostatin, prostaglandin and acetylcholine.[40] Studies by Wallengren et al.[64] demonstrated that topical pretreatment with capsaicin enhances different experimental inflammations, including allergic dermatitis. 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.

Chlorobenzylidene malononitrile (CS). Chlorobenzylidene malononitrile is a primary irritant that elicits injurious action on the skin when applied topically either as a powder or as a solution or on exposure to CS aerosol.[65–68] At areas of clothing contact, excessive perspiration may contribute to the development of dermal lesions. Gutentag et al.[65] and Bowers et al.[66] reported the occurrence of erythema and vesiculation in human subjects topically exposed to CS powder or CS solution. Exposure to CS aerosols at a concentration of 300 mg m^{-3} for 45 min produced erythema and vesiculation; however, skin lesions were not evident at an exposure duration of

30 min.[69] 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. Rothberg[68] confirmed that both CS and CN could produce skin sensitization in guinea pigs when administered topically and intradermally. Fuchs and in der Wiesche[70] conducted patch testing of individuals who had been exposed to CS or CN during civil disturbances. Skin symptoms were reported in over 50% of the individuals exposed and positive test reactions to CS and CN were observed.

Dibenz[b,f]1:4-oxazepine (CR). The effects of CR on the skin are generally limited to the production of transient erythema, and contact with CR does not induce vesication or contact sensitization or delay the healing of skin injuries.[29,71,72] The burning sensation on exposure to CR persists for 15–30 min and erythema may last for 1–2 h. Considerable interest in the cutaneous effects of sensory irritant compounds has led to several studies on the dermal effects of CR in humans.[57,72,73] Weigand and Mershon[73] studied the dermal effects of dilute CR and CS solutions. Test subjects were patch tested on various anatomical sites with concentrations of test article ranging between 0.01 to 1.0%; exposure duration was for 5 or 30 min. A stinging sensation was evident on 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 degree was evident, which subsided within 4 h. Holland[72] evaluated skin reactions to CR in humans after application of varying amounts of CR as a powder or as dry material moistened with saline. Erythema was noted in 10 min, which faded on removal of test article; when moistened, CR produced 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[72] concluded that all reactions to CR were mild and transient compared with that of CS, which resulted in an erythema of greater duration, and with that of CN, which produced blistering. Ballantyne and co-workers[74] drenched volunteer subjects with very dilute solutions of CR and CS for durations of 15 and 60 s. In the studies comprising subjects that were exposed individually, stinging of the skin around the eyes was rapid in onset, which spread to other parts of the face. The burning sensation involving facial skin was the next pronounced feature for approximately the first minute. Scalp and ears usually were not 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 at 3–4 min and the burning sensation was intense by ~5 min. Other anatomical sites (e.g. chest, abdomen, thighs and buttocks) were affected at ~5 min. The burning sensation of the skin was intense, primarily affecting the trunk and back at ~10 min. Approximately 15 min from the onset of exposure the skin sensation had subsided. By 20 min the skin sensations were reduced to mild tingling or had disappeared. Erythema of the skin was produced within several minutes and persisted for 1–2 h; no other skin effects were noted. Many areas of the skin were rather 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) to that seen with the CR drenches. The studies by Ballantyne and co-workers[74] demonstrated that very dilute solutions of CR and CS produce a strong stimulation of sensory receptors in the skin and mucous membranes. 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.

Chloroacetophenone (CN). Exposure to CN has been associated with primary irritation and allergic contact dermatitis.[75–78] It is a potent skin irritant and is more likely to cause serious effects of the skin compared with that induced by CS or CR. 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.[77]

Adamsite (DM). Skin effects include erythema and local application can produce skin necrosis. Adamsite is not a skin sensitizer based on studies by Rothberg.[68]
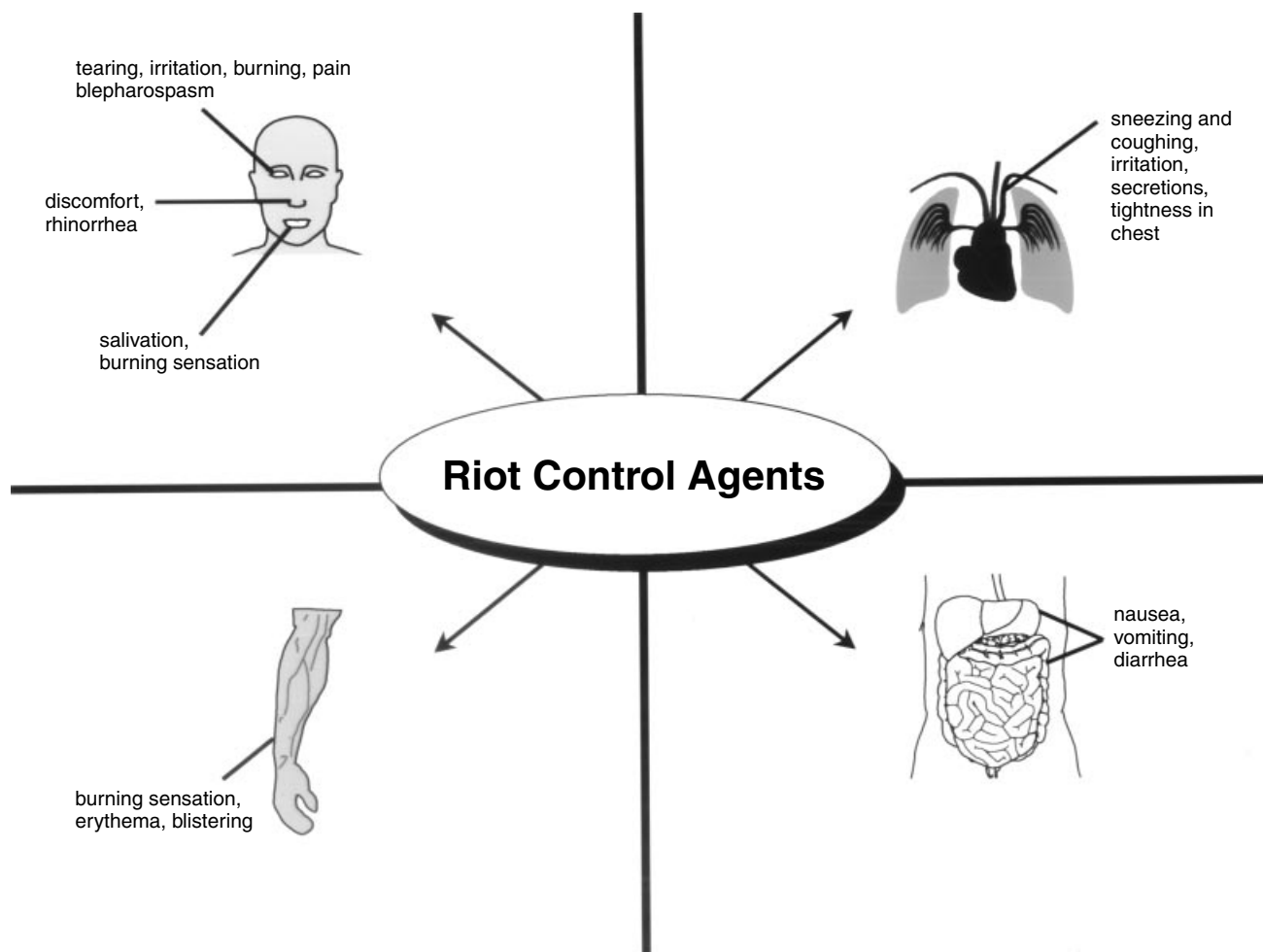
TOXICOLOGY OF RIOT CONTROL AGENTS

Riot control agents, generally regarded as having low toxicity, are potent sensory irritants that elicit acute site-specific toxicity (see Fig. 2 and Tables 3 and 4). These agents have been described as non-lethal. Exposure to riot control agents may occur via inhalation, dermal and oral routes of exposure. These compounds primarily act on the eye, which is the most sensitive target organ; however, the majority of these compounds also will affect the pulmonary system and the skin. Riot control agents can cause some or all of the effects on these target organs to a greater or lesser extent. Effects immediately produced 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 causing an intolerable effect and that which may cause serious adverse responses is large. For instance, the lethal quantity for the tear agent CS is estimated to be ~2600 times as great as the dosage necessary to cause temporary disabling. Permanent adverse effects usually do not accompany riot control agents; however, the risks for deleterious effects, long-term effects or even lethality increase with higher exposure levels and/or greater exposure times. The acute and short-term

Figure 2. Acute site-specific toxicity of riot control agents.

repeated-dose toxicity of riot control agents have been studied adequately; however, the extent of our knowledge concerning the long-term and chronic toxicity of these compounds is somewhat limited. The animal and human toxicology of modern riot control agents (CS, CR, CN, DM and OC) is presented. Topics covered include comparative toxicology, dose–effect relationships, target organ effects, low-dose toxicity, biochemistry and mechanism(s)/interactions.

Mammalian toxicology: acute toxicity

Oleoresin capsicum (OC) and capsaicin. Oleoresin capsicum (OC) is obtained from pepper plants and is a mixture containing capsaicinoids, including the active ingredient capsaicin (8-methyl-N-vanillyl-6-nonenamide) and other compounds. A highly effective irritant, OC has received much attention as a less-than-lethal agent within civilian, governmental and military sectors. The OC spray ('pepper spray') has gained popularity as a police weapon in recent years. Oleoresin capsicum is a natural product and is generally considered safe, which is a viewpoint that is not necessarily accurate. It has been incorporated into various formulations and marketed as 'pepper spray', 'pepper gas' and 'pepper mace' for law enforcement, civil disturbance control purposes, criminal incapacitation and self-defense. As a spray, OC quickly produces lacrimation and involuntary closure of the eyes. It also elicits respiratory-related responses such as nasal irritation, bronchoconstriction, severe coughing and sneezing and shortness of breath. Oleoresin capsicum additionally causes burning sensation of the skin and neuromotor dysfunction (i.e. loss of motor control). Consequently, exposed individuals in most cases can be subdued easily. Acute effects of capsaicin and capsaicinoids are associated chiefly with the pulmonary system (e.g. bronchospasm, respiratory arrest, pulmonary edema) but also may encompass hypertensive crisis and hypothermia. Suprathreshold levels of capsaicin can result in serious respiratory and cardiovascular effects, as well as permanent damage to the sensory nervous system. There have been a considerable number of deaths related to OC use. Although a causal relationship has not been established, most of the reported deaths have occurred within an hour after exposure. Additional information on the chemistry, pharmacology, toxicology and physiology of OC, capsaicin and capsaicinoids can be found in numerous articles and reviews.[14,40,79–94]

As early as the 1920s, capsaicin was prepared for evaluating the physiological and pharmacological effects in humans. Interest in the development of capsaicin as a riot control agent waned as research efforts were directed to understanding the biological actions of the newly synthesized agent CS. Unlike other lacrimatory agents such as CN, CR and CS, which have definite chemical compositions, OC is a mixture of compounds containing

capsaicin and its structural analogs, various acids and esters, alcohols, aldehydes, ketones and carotenoid pigments.[95–99] Numerous compounds in OC have been identified via gas chromatography–mass spectrometry (GC-MS) by Keller et al.[100] The capsaicinoid content of the dried fruit has been reported to range from 0.1 to 1%.[89] The capsaicinoid content of the oleoresin is as follows: capsaicin ($\sim$ 70%), dihydrocapsaicin ($\sim$ 20%), norhydrocapsaicin ($\sim$ 7%), homocapsaicin ($\sim$ 1%) and homodihydrocapsaicin ($\sim$ 1%). Because capsaicin is the principal active ingredient of OC, little consideration has been given to the other capsaicinoids with regard to their biological effects and mechanism(s) of action. Generally, these analogs have effects similar to capsaicin, although with different potencies.[99]

Toxicological studies have been conducted on both capsaicin and OC; however, despite extensive field application, few formal evaluative studies of OC have been conducted. Because OC is a much-utilized food component, it is widely regarded as safe with a low degree of toxicity.[101] Overall, data on the toxicology of OC is extant, particularly regarding effects following exposure to OC via inhalation. Recent inhalation studies on OC have indicated that the toxicity of OC may be minimal following inhalation exposure. (R. Mioduszewski, 1997, unpublished data; Ref. 102). Debarre and co-workers[102] conducted nose-only inhalation exposures in rats to ascertain the effects of aerosolized OC and various solvents. Pulmonary physiology parameters were evaluated to determine alterations in respiratory function as well as histopathological evaluation of pulmonary tissues. The salient finding following exposure to OC was a decreased minute volume. Histopathological changes included interstitial edema of the lungs and epithelial lesions of the trachea. Debarre et al. suggested that additional studies are needed using an animal model of bronchial hyperresponsiveness (i.e. rat; see Ref. 103) to assess better the risk of individuals with compromised pulmonary function to riot control agents and irritant chemicals.

The pharmacological and toxicological effects of capsaicin are far better characterized than that of OC. In vivo, the severity of toxic effects depends on factors such as route of administration, the dose of capsaicin and the age of the animal. Pertaining to capsaicin toxicity, Glinsukon et al.[104] have derived LD_{50} values for capsicum extracts and capsaicinoids. Representative values for capsaicin are 0.56 mg kg^{-1} i.v., 7.6 mg kg^{-1} i.p., 7.8 mg kg^{-1} i.m., 9.0 mg kg^{-1} s.c., 190 mg kg^{-1} intragastric, 512 mg kg^{-1} dermal and 1.6 mg kg^{-1} intratracheal. It was noted that the toxicity of capsaicin in the capsicum extract was about four fold greater than that of pure capsaicin administered intraperitoneally. Findings indicated that guinea-pigs were more susceptible than mice or rats, whereas hamsters and rabbits were less vulnerable to the toxic actions of capsaicin. The most likely cause of death was respiratory paralysis.

Pharmacological and toxicological studies—to include inhalation exposures—have contributed to a better understanding of capsaicin-induced effects and actions on the living organism. The multi-varied pharmacological actions of capsaicin and capsaicinoids were characterized in the 1950s[105–109] and further elucidated in the 1980s (for reviews, see Refs 40 and 110–112). Capsaicin has a spectrum of effects on sensory neurons, ranging from excitation to cell death, and as stated previously suprathreshold

amounts of capsaicin can cause irreversible damage to the sensory nervous system.[87,91,113–133] The functions of capsaicin-sensitive sensory neurons, representative therapeutic applications of capsaicin and pathophysiological implications following treatment/exposure to suprathreshold doses are highlighted in Table 5. It has been assumed generally that capsaicin's neurotoxic effects are limited to sensory neurons with small-diameter unmyelinated afferent processes[40,111,112,145–150]; however, findings reported by Ritter and co-workers[151–155] suggest that capsaicin-induced neurotoxicity is more widespread in the nervous system than previously assumed. Systemic administration of capsaicin produces degeneration of cell bodies, axons and nerve terminals at specific sites throughout the entire neuroaxis. Capsaicin has been used as a selective probe to study the role of neurogenic inflammation, a phenomenon resulting from stimulation of certain types of sensory nerves, producing vasodilatation and extravasation. Reference to this condition as neurogenic inflammation is attributed to Jancso[156] and has been the object of extensive research—the reader is referred to Refs 112–114, 147, 150, 157–162. Capsaicin also has been used to elucidate the role of nociceptors and has gained the status of an invaluable tool in sensory neuron research.

In addition to capsaicin-induced effects on thin sensory neurons, capsaicin exerts action on non-sensory neurons and non-neural excitable cells. The cell non-selective effects of capsaicin include inhibition of cardiac muscle excitability,[163,164] inhibition of visceral smooth-muscle activity[165,166] and contraction of vascular smooth muscle.[167,168] In addition, capsaicin has been reported to

Table 5—Functions of capsaicin-sensitive sensory neurons, pathological implications of capsaicin exposure and clinical applications

Functions of capsaicin-sensitive sensory neurons	
Visceral afferents	**Somatic afferents**
Afferent function	**Afferent function**
Nociception and reflex homeostasis	Nociception and reflex homeostasis
Cardiovascular regulation	Cardiovascular regulation
Efferent function	**Efferent function**
Neurogenic plasma extravasation	Neurogenic plasma extravasation
Vascular control	Modulation of inflammatory reactions
Mucous secretion	Antidromic vasodilatation
Smooth-muscle contraction	
Pathological implications of capsaicin damage	**Representative clinical applications of capsaicin**
Reduced response in detecting noxious stimuli and loss of homeostasis	Ablation of skin inflammatory responses (i.e. whealing)
Weakened resistance of tissue (i.e. gastric) to injurious stimuli; altered gastric mucosal defense mechanisms	Treatment of urogenital dysfunction (i.e. bladder hyperreflexia)
Skin pathophysiology as a result of altered blood flow and vascular permeability	
Corneal opacities	

Pathological implications from Refs 134–142; clinical applications from Refs 142–144.

influence various metabolic processes.[169] Importantly, the cell non-selective effects of capsaicin are usually produced by concentrations of capsaicin that are far in excess of those needed to stimulate sensory neurons.

The airway mucosa is highly sensitive to capsaicin and exposure to this substance leads to intense irritation, which in severe cases is highly painful to the nasal passages.[170] In the nasal passages, activation of capsaicin-sensitive sensory nerves results in profound vasodilation, secretion, and increased nasal mucosal volume. Capsaicin markedly influences pulmonary function and mechanics, and the pulmonary toxicology of capsaicin has been studied in some detail. Capsaicin activates protective reflexes such as avoidance[40,148,171] or bronchoconstriction, sneezing, coughing and apnea and rapid shallow breathing in response to airway irritation.[172–175] Apnea followed by rapid shallow breathing is the classical chemoreflex response on stimulation of sensory neurons in the lung. All of the aforementioned reflexes function to restrict access of irritant material to lower airways. Furthermore, activation of sensory neurons of the upper and lower respiratory tract is associated with increased vascular permeability to plasma proteins in the airway mucosa.[176] Other reflexes involve cardiovascular,[177–179] neuroendocrine[180] and thermoregulatory[120,181,182] control mechanisms. Capsaicin may induce the Kratschmer reflex, which on inhalation of an irritant causes cardiorespiratory dysfunction, which is characterized as consisting of apnea, bradycardia and a biphasic fall and rise in aortic blood pressure.

The bronchoconstriction and airway mucosal edema manifested in laboratory animals and humans exposed to capsaicin are phenomena associated with the release of the neuropeptide substance P from sensory nerve terminals.[183–189] The involvement of substance P in capsaicin-induced physiological effects is discussed in a subsequent section on mechanisms of action and interactions. In addition to the depletion of substance P, there is also depletion of other neuropeptides from primary sensory neurons, namely, neurokinin A (NKA), calcitonin gene-related peptide (CGRP), somatostatin (SOM), and kassinin, as revealed by immunohistochemistry and radioimmunoassay.[175,190–199] The pulmonary system effects of capsaicin are species-related. In the guinea-pig, intravenous and intra-arterial dosing causes bronchoconstriction.[200] In the dog and cat, intravenous dosing 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.[201] Studies designed to elucidate the mechanism by which aerosolized capsaicin causes bronchoconstriction in guinea-pigs suggest that a vagal/cholinergic and non-cholinergic local axon reflex contribute to this effect.[202]

Capsaicin induces complex effects on the cardiovascular system: tachypnea, hypotension (seen in the Bezold–Jarrish reflex), bradycardia, and apnea. The cardiorespiratory effects of capsaicin have been studied following intravenous dosing. Capsaicin treatment resulted in a triphasic effect on blood pressure and altered cardiac parameters.[203,204]

Perturbations in thermoregulation can result after exposure to capsaicin and capsaicinoids[105,106,205–213]—for an authoritative review, see Ref. 120. Capsaicin has been used for the last 25 years as the tool of

choice in elucidation of the physiological processes underlying the control of body pain and temperature. It has been demonstrated that pretreatment/treatment of animals with capsaicin results in severely impaired heat escape behavior and induces an irreversible impairment in thermoregulation.[205,206,212,214,215] In elevated environments, body temperature rose concomitant with an inability to discriminate and seek cooler environments.[212] Additionally, 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. Szolesanyi[212] also noted that s.c. administration of capsaicin reduced body temperatures, and that the dosing regimen resulted in a tolerance to thermal regulation. Studies by Frens[216] demonstrated that s.c. injections of capsaicin decreased body temperature in goats. On the subject of nociceptors, Konietzny and Hensel[130] demonstrated that topical treatment of human skin with 1% capsaicin and capsaicinoids lowered the threshold to thermal pain. The collective data regarding capsaicin-induced perturbations of thermoregulation support the notion that capsaicin and capsaicinoids have potentially adverse physiological consequences to individuals exposed to these substances at elevated temperatures as well as under conditions involving repeated-dose scenarios.

The effects of capsaicin and capsaicinoids on the gastrointestinal tract and nutritional impacts also have been examined.[217–221] The duodenal mucosal response to capsaicinoids and altered fat uptake by damaged duodenal epithelium, as reported by Nopanitaya[217] and Nopanitaya and Nye,[218] has led to subsequent studies on the alteration of nutrient absorption and metabolism by capsaicinoids. Studies by Sambaiah et al.,[219,222] and Kawada et al.,[220] indicated that capsaicinoids had no adverse effect on fat intake or absorption. The lipotropic and hypolidemic effects of capsaicinoids also have been examined in some detail.[220,223,224] Sambaiah and Satayanarayana[224] had postulated that capsaicinoids counteract the accumulation of fat in the liver by the reduction of hepatic lipogenesis and/or increased oxidation of lipids.

Repeated administration of capsaicin produces systemic desensitization to chemogenic and thermal nociceptive stimulation.[183,225–230] Desensitization may be considered as the initial manifestation of the long-term neurotoxic action of capsaicin on sensory neurons. It implies a readily reversible functional refractoriness in the absence of morphological changes. Alterations in neurophysiology concomitant with morphological changes are generally viewed as implying neurotoxicity. Experimental data suggest that exposure to high doses of capsaicin and its analogs results in long-lasting insensitivity to stimuli such as irritants, pain and temperature.[89] Capsaicin-induced desensitization, which may be manifested for weeks, is associated with reversible structural changes. Long-term effects involving the pulmonary system are characterized by desensitization of the airways to chemical irritants and the marked inhibition of vagal bronchoconstriction effects.[186] It is postulated that capsaicin-induced desensitization is caused by acute and excessive depletion of the neurotansmitter substance P, which is expressed as a lack of normal physiogical response to stimuli such as heat and cold. High doses of systemic capsaicin produce a permanent or long-lasting desensitization of capsaicin-sensitive afferent nerves in newborn rats. In adult rats,

the same doses elicit a long-lasting but temporaneous block of the nerves. In both instances, transmission of pain in response to various noxious stimuli was inhibited or abolished in animals dosed with capsaicin. The effect is postulated to be capsaicin-induced and the resulting neurodegeneration of C-fiber receptors.[183] More recent findings suggest that this effect can be dissociated by using lower doses.[231]

Chlorobenzylidene malononitrile (CS). The compound *o*-chlorobenzylidene malononitrile, first synthesized in 1928, is an extensively used tear gas. It is commonly know as CS and is named after the initials of the two British chemists who synthesized a number of benzylidene malononitriles, including CS.[28] The riot control agent CS was developed in the 1950s as a potent and safe riot control agent, and the US. Army adopted CS as their standard riot control agent in 1959. It is regarded as a potent and generally safe riot control agent, yet as with this class of compounds high air concentrations can lead to toxic reactions in experimental animals and humans.[26,42,232] It has been studied extensively in animals and humans and has been widely used around the world with no verified deaths in humans following its use. Like CN and DM, CS 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. A micronized formulation of CS is CS2, which consist of 95% CS, 5% Cab-o-Sil® (Cabot Corp.) and 1% hexamethyldisilazane. The additives prevent agglomeration and produce a free-flowing powder that can be dispersed from powder formulation devices.[61]

Chlorobenzylidene malononitrile, a peripheral sensory irritant, is highly irritating to mucous membranes that cover or line tissues of the eyes, nose, throat and stomach. Ocular effects of CS include intense irritation, excessive tearing, conjunctivitis, discomfort and pain and uncontrolled blinking (blepharospasm). The nose and mouth may perceive a stinging or burning sensation concomitant with excessive rhinorrhea or discharge of nasal mucous. Irritation of the respiratory tract, prevalent following CS exposure, is also associated with sneezing and coughing, increased tracheobronchial secretions and tightness of the chest. Severe lung injury and consequent respiratory and circulatory failure characterize death in experimental animals after inhalation of CS. Irritation of the gastrointestinal tract may cause vomiting and/or diarrhea. Exposure of the skin to CS results in a burning sensation, which may be followed by inflammation and erythema. The skin effects may be more severe and result in blistering, particularly when exposure occurs in hot and humid conditions. Within 30 s of exposure some or all of the aforementioned effects may occur and subside and/or disappear within minutes on cessation of exposure. The irritation during exposure is so great that it causes an exposed individual to seek escape from the exposure. The lethal effect of CS by inhalation is due to lung damage, which leads to asphyxia and circulatory failure. Bronchopneumonia secondary to respiratory tract injury also may be a cause of death. Pathological changes involving extrapulmonary tissues (e.g. liver and kidneys) following exposure to high concentrations of CS are secondary to respiratory and circulatory failure. The

reader is referred to numerous publications concerning the animal and human toxicity of CS.[29,42,74,102,232–239]

The pharmacology of CS has been studied by Biscoe and Shephard[240] and Brimblecombe *et al.*[241] Brimblecombe and co-workers investigated the pharmacological actions of CS (pure or pyrotechnically generated) administered by various routes to animals and when applied to isolated organs and tissues. Following i.v. administration, a typical response to CS was a rise in arterial blood pressure. Qualitative and quantitative species differences were noted following CS treatment; for example, dogs appeared less sensitive than cats to the cardiovascular effects of CS. Animals exposed via inhalation to pyrotechnically generated CS manifested changes in respiratory parameters. A number of studies have been conducted to characterize the acute toxic effects of CS, which included incapacitating studies by aerosol or vapor exposure as well as skin and eye irritation studies. The inhalation toxicity of chemical warfare agents, military chemicals and riot control agents is, by convention, expressed by the notation Ct. It is defined as the product of the concentration in $mg\ m^{-3}$ multiplied by the exposure time (t) in minutes ($mg\cdot min\ m^{-3}$). The terms LCt_{50} and ICt_{50} describe the airborne dosages that are lethal (L) or incapacitating (I) to 50% of the exposed population. A number of animal studies on CS have been reviewed and summarized in a report by McNamara *et al.*[61] Various animal species were exposed for 5–90 min to CS aerosols that were generated using various dissemination techniques. 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 nearly all species. Goats, pigs and sheep did not manifest hyperactivity on exposure to the test article. The heightened activity that was observed initially subsided rather quickly, and by 5–15 min from the start of exposure the animals exhibited lethargy and pulmonary stress. These latter effects continued for ~1 h on cessation of exposure. All other signs had abated within 5 min on removal from the exposure atmosphere. When toxic signs were noted, these occurred following exposure via all dispersion methods. Lethality estimates (expressed as LCt_{50}) from acute exposures to CS dispersed from 10% CS in methylene dichloride are as follows: rats, $1\,004\,000\ mg\cdot min\ m^{-3}$; mice, $627\,000\ mg\cdot min\ m^{-3}$; and guinea-pigs $46\,000\ mg\cdot min\ m^{-3}$. No deaths occurred in rabbits exposed to CS dosages of up to $30\,000\ mg\cdot min\ m^{-3}$. Dosages up to $30\,000\ mg\cdot min\ m^{-3}$ were not lethal to monkeys, including those that had associated pulmonary dysfunction (i.e. pulmonary tularemia). The combined LCt_{50} for CS dispersed from methylene dichloride for rats, mice, guinea-pigs and rabbits was calculated to be $1\,230\,000\ mg\cdot min\ m^{-3}$. The order of sensitivity of various animal species to molten CS is guinea-pig > rabbit > rat > dog > mouse > monkey. The results from acute exposures to CS (sprayed as molten agent) are presented in Table 6. Because of their resistance to the lethal effects of CS, LCt_{50} values could not be calculated for swine, sheep and goats. However, the combined LCt_{50} for mice, rats, guinea-pigs, rabbits, dogs, monkeys, swine, sheep and goats was estimated to be $300\,000\ mg\cdot min\ m^{-3}$.

The results (LCt_{50}) from acute exposures to CS dispersed from M18 thermal grenades are $164\,000\ mg\cdot min\ m^{-3}$ for rats and $36\,000\ mg\cdot min\ m^{-3}$ for guinea pigs. The order of sensitivity to thermally-generated CS is swine > dog

Table 6—Acute toxicity estimates for CS

Species	LCt$_{50}$ (mg·min m^{-3})
Guinea-pig	8 000
Rabbit	17 000
Rat	32 000
Dog	34 000
Mouse	42 000
Monkey	50 000

The LCt$_{50}$ values have been rounded off.

> rabbit > goat > guinea-pig > rat > monkey. Results from acute exposure to CS dispersed from M7A3 thermal grenades are summarized in Table 7.

Combining the results from all of the acute exposures, the LCt$_{50}$ values are as follows: all non-rodents combined 36 000 mg·min m^{-3}; all rodents combined, 79 000 mg·min m^{-3}; and all species combined, 61 000 mg·min m^{-3}. The inhalation toxicity of CS2, which comprises 95% CS, 5% Cal-o-Sil®, and 1% hexamethyldisilazane, also has been evaluated. The results (LCt$_{50}$) from acute exposure to CS2 are as follows: rats, 68 000 mg·min m^{-3}; guinea-pigs, 49 000 mg·min m^{-3}; dogs, 70 000 mg·min m^{-3}; and monkeys, 74 000 mg·min m^{-3}.

Cucinell et al.[242] reported the physiological and toxicological effects of CS in rats and dogs exposed to CS aerosol. Because lungs of animals exposed to riot control agents manifest edema, hemorrhage and atelectasis, studies in rats were conducted to assess the surfactant and lysosome activity from lung washings of CS-exposed rats. In these studies, rats were exposed to CS aerosols at Ct values that ranged from 40 000 to 80 000 mg·min m^{-3}. The findings indicated an increase in the surface tension of the saline washouts of lungs from CS-exposed animals. Analysis of lung lavage fluid from CS-exposed animals indicated an increase in β-glucuronidase, suggestive of lysosomal activity following injury to the pulmonary tract. Dogs were exposed to CS aerosol at either a low or a very high concentration of test article. In the low-dose segment, the face of the animal was exposed to an airborne concentration of 25 µg l^{-1} of CS for 30 s. In the high-dose study, the animals were exposed to an aerosol concentration of 2300 µg l^{-1} for 23 min, which was equivalent to a Ct of 57 000 mg·min m^{-3}. Physiological effects noted on exposure to the low level of CS aerosol consisted of alterations

Table 7—Acute toxicity estimates for CS (grenade)

Species	LCt$_{50}$ (mg·min m^{-3})
Swine	17 000
Dog	30 000
Rabbit	38 000
Goat	48 000
Guinea-pig	66 000
Rat	94 000
Monkey	120 000

The LCt$_{50}$ values have been rounded off.

in respiratory patterns and an increase in blood pressure. The pattern of response observed was suggestive of the Sherrington pseudoaffective response.[243] Exposure to very high levels of CS aerosol resulted in respiratory stress and mortalities; however, details were not given. Debarre and colleagues[102] conducted nose-only inhalation studies on CS. Results indicated altered lung physiology (i.e. decreased minute ventilation) and histopathological of changes (e.g. cytoplasmic vacuoles and areas of emphysema).

Dibenz[b,f]1 : 4-oxazepine (CR). A more recent addition to the riot control family of compounds is CR, first synthesized in 1962. It is a potent sensory irritant of low toxicity. The irritating effects on the eye and skin irritation are more transitory than those of other riot control agents such as CS. Vesication or contact sensitization are not associated with CR exposure.

It has low acute toxicity, as demonstrated in various animal species exposed to CR via different routes—the data are summarized by Ballantyne.[29,71] The LD$_{50}$ and LCt$_{50}$ values for CR and other commonly used riot control agents are summarized in Table 8. Ballantyne[71] demonstrated that CR, by all routes of exposure, is less toxic than CN or CS. Animals dosed with CR manifest rapid breathing, ataxia (incoordination), spasms and convulsions. Generally, these effects gradually subside over a 15–60 min period, after which time the animals appear normal or there is marked respiratory distress and death. Pathological changes noted in i.v. and orally dosed animals consisted of congestion of alveolar capillaries and liver sinusoids. No histological abnormalities were noted in CR-treated animals following intraperitoneal administration of CR. Compound-related effects included muscle weakness and heightened sensitivity to handling. Toxic effects persisted through the first day after exposure and some animals exhibited CNS effects. Animals surviving the post-exposure period exhibited no gross or histological abnormalities at necropsy. Ballantyne[71] also studied the effects of CR in various animal species following inhalation exposure. Animals were acutely exposed to CR aerosol or CR smoke for varying exposure times and at different concentrations of test article. Rats exposed to CR aerosol at Ct values ranging from 13 050 to 428 400 mg·min m^{-3} manifested nasal secretions and blepharospasm (uncontrollable closure of the eyelids), which subsided within 1 h on cessation of exposure. Mortalities had not occurred among the CR-exposed rats. In rabbits, guinea-pigs and mice exposed to CR aerosol, no deaths occurred at Ct values up to 68 400 mg·min m^{-3}. Exposure to pyrotechnically generated CR resulted in alveolar capillary congestion and intra-alveolar hemorrhage, as well as congestion of the liver and kidneys.

The potential of CR aerosol to produce physiological and ultrastructural changes of the lung was studied by Pattle and co-workers.[244] In these studies, rats were exposed to high dosages of CR aerosol (Ct = 115 000 mg·min m^{-3}). Electron microscopy examination revealed that organelles (i.e. lamellated osmiophilic bodies) were not altered as a result of exposure to CR. In studies by Colgrave et al.,[245] the effects of high CR aerosol dosages (78 200, 140 900 and 161 300 mg·min m^{-3}) on the pulmonary system were evaluated. The lungs appeared

Table 8—Comparative toxicity of CR[a], CS[b] and CN[b]: LD_{50} (a) and LCt_{50} (b)

Route	Species	CR	CS	CN
(a) LD_{50} (mg kg^{-1})[c]				
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
(b) LCt_{50} (mg·min m^{-3})[c]				
Inhalation	Mouse	203 600	76 000	—
(pyrotechni-	Rat	139 000	68 000	23 000
cally	Rabbit	160 000	63 000	15 800
generated)				
Inhalation (aerosol)	Mouse	169 500	67 200	18 200–73 500[d]
	Rat	428 400	88 460	3700–18 800[d]
	Rabbit	169 000	54 100	5840–11 480[d]
	Guinea-pig	169 500	50 010	3500–13 140[d]

[a] Data from several sources as reported by Ballantyne.[29]
[b] Data from several sources as documented in a report by the National Academy of Sciences.[6]
[c] Lowest value reported.
[d] Range of values from several sources.

normal on gross examination; however, microscopic examination revealed mild congestion, hemorrhage and emphysema. Electron microscopy identified isolated swelling and thickening of the epithelium and early capillary damage, as evidenced by ballooning of the endothelium. Colgrave and co-workers concluded that very high doses of CR aerosol produced only minimal pulmonary damage.

The effects of intravenously administered CR on the cardiovascular system were studied by Lundy and McKay[246,247] and Lundy.[248] A dose-dependent increase in blood pressure of short duration was observed. Stimulation of the heart rate and increased arterial catecholamine content also were noted following treatment with CR. The authors postulated that the CR-induced cardiovascular response was associated with sympathetic nervous system effects, as evidenced by abolition of the CR-induced pressor effect by phentolamine and 6-hydroxydopamine.

Chloroacetophenone (CN). Chloroacetophenone, a white crystalline solid with an apple-blossom odor, is commonly known as tear gas or Mace® and has the military designation CN. First synthesized in 1871, chloroacetophenone was studied for its use as a tear gas shortly after World War I. It acts directly on the mucous membranes to produce intense ocular and respiratory irritation and associated burning and pain sensation of the eyes, nose, throat and lungs. Ocular effects consist of 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 up to 20 min after removal from the contaminated atmosphere.

Acute and repeated-dose inhalation studies have been conducted in various animals to ascertain the comparative toxicity of CN. The toxicology of CN has been reviewed and summarized by McNamara et al.,[61] National Academy of Sciences in a report[6] and by Hu et al.[249] Early toxicity studies on CN were highly variable, and studies subsequently conducted in the mid-1960s in various 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 noted on exposure to CN consisted of lacrimation, conjunctivitis, copious nasal secretions, salivation, hyperactivity, dyspnea and lethargy. Cutaneous effects seen in the exposed animals consisted mainly of erythema. The salient biological finding exhibited by all exposed animals on post-exposure was dyspnea. Ocular effects (i.e. conjunctivitis) and dermal effects (i.e. erythema) persisted for 3–7 days after exposure. The primary cause of death following CN inhalation was from the injurious action of CN on the pulmonary system. The LCt_{50} estimates for CN in various species are as follows: rat, 8878 mg·min m^{-3}; guinea-pig, 7984 mg·min m^{-3}; and dog, 7033 mg·min 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 pathology reported by Ballantyne and Swanson[238] in animals that died after CN inhalation included congestion of the alveolar capillaries, alveolar hemorrhage and excessive secretion in the bronchi and bronchioles. There were also areas of acute inflammatory cell infiltration of the trachea, bronchi and bronchioles.

Diphenylaminochloroarsine (adamsite, DM). As discussed previously, riot control agents may be classified

according to type (e.g. lacrimators, vomiting agents, sternutators) based on a salient physiological effect. Diphenylaminochlorarsine (DM) is one of several compounds classified militarily as vomiting agents, including diphenylchloroarsine (DA), diphenylcyanoarsine (DC), and chloropicrin. It has been categorized as both a vomiting agent and sternutator and was known as adamsite during the World War I. It has been used also as a riot control agent and, according to Cookson and Nottingham,[12] only by the USA. It is more toxic than other riot control compounds and is considered a potentially dangerous agent. As reported by Sidell,[17] the estimated human LCt_{50} is 11 000 mg·min m^{-3}. It produces symptoms of slightly delayed onset and a relatively long recovery period. The DM-related effects do not appear immediately as in the case of riot control agents CN, CS, and CR. The DM-induced responses occur in ~3 min after the start of exposure and, depending on the severity of the exposure, the effects may last for up to several hours.[29,250] Unlike other lacrimatory compounds, DM is more likely to cause prolonged systemic effects. Signs and symptoms of DM exposure include eye irritation, upper respiratory tract irritation, uncontrolled sneezing and coughing, choking, headache, acute pain, tightness in the chest, nausea and vomiting. In addition to these effects, DM can cause unsteady gait, weakness in the limbs and trembling. Ballantyne[29] has drawn attention to mental depression as a prominent symptom following exposure to DM. Exposure to high concentrations of this material can result in serious illness as a result of pulmonary damage and edema or death.[250]

A number of investigations on the physiological effects of DM in various species of animals, including primates, have been conducted and the findings are summarized in reviews by McNamara et al.[61] and Owens et al.,[251] as well as in a National Academy of Sciences report.[6] Acute exposure to DM results in hyperactivity, ocular and nasal irritation, salivation, labored breathing, ataxia and convulsions. Punte and co-workers[60] have reported the acute inhalation effects of high aerosol concentrations of various irritant compounds, which included DM. Toxic signs observed in animals were hyperactivity, ocular and nasal irritation, lacrimation, salivation, respiratory distress and lethargy. Histopathological examination revealed no abnormalities below an inhaled dosage of 500 mg·min m^{-3} of DM. The LCt_{50} estimates were as follows: rat, 3700 mg·min m^{-3}; mouse, 22 400 mg·min m^{-3}; and guinea-pig, 7900 mg·min m^{-3}. The authors also computed the theoretical dose (inhaled LD_{50}) received, which was calculated from the respiratory volume, the LCt_{50} and the estimated percentage retention. The computed inhaled LD_{50} values for DM are as follows: rat, 14.1 mg kg^{-1}; mouse, 17.9 mg kg^{-1}; and guinea-pig, 2.4 mg kg^{-1}. Animals exposed to DM at a dosage of 500 mg·min m^{-3} did not exhibit pathological changes. Animals sacrificed or dying after exposure to DM manifested hyperemia of the trachea, pulmonary congestion and edema and pneumonia. The clinical and pathological findings are in concordance with those observed on exposure to other pulmonary irritants. Striker and co-workers[252] studied the effects of DM in monkeys exposed to test article at varying concentrations and exposure periods: 855 mg m^{-3} for 3 min; 1708 mg m^{-3} for 5 min; and 2615 mg m^{-3} for 11 min. At the lowest exposure, toxic effects were limited to a single animal that exhibited a diminished response to stimuli and oral and nasal discharge. Exposure to a Ct of 8540 mg·min m^{-3} produced ocular and nasal irritation, conjunctival congestion, facial erythma and decreased responses—all signs had abated by 24 h. Exposure to a Ct of 28 765 mg·min m^{-3} resulted in hyperactivity, conjunctival congestion, copious nasal discharge, marked respiratory distress, gasping and gagging in all animals exposed. In the high exposure group, eight deaths had occurred within 24 h. Necropsy of the high dose group revealed congested and extremely edematous lungs, and microscopic examination revealed ulceration of the tracheobronchial tree and pulmonary edema. Additional studies in monkeys also were conducted by Striker et al.[253] In these studies, the effects of 'low' concentrations of DM were evaluated. Animals were exposed to DM at target concentrations of 100 and 300 mg m^{-3} for exposure periods of 2–60 and 2–40 min respectively. A progression of toxic signs, characteristic of irritant gases, were seen as the exposure times were increased. At the maximum Ct of 13 200 mg·min m^{-3}, animals exhibited conjunctival congestion oral and nasal discharge and nausea and vomiting. At Ct values of <1296 mg·min m^{-3}, responses were limited to blinking. Serious effects involving the eyes have been characterized as necrosis of the corneal epithelium on exposure to DM.[39]

Repeated-dose toxicity

Capsaicin and capsaicinoids. The bulk of available toxicological data on the effects of repeated dosing of capsaicin and capsicum was reported by Lee,[254,255] Nopanitaya[256] and Monsereenusorn.[257] Multiple dosing of capsaicin and capsicum in the rabbit resulted in pathological alterations in several organ systems.[254,255] In the study reported by Lee,[254] capsaicin resulted in hepatic necrosis following multiple-dose administration. Mice fed a diet containing capsicum extract for 4 weeks did not exhibit signs of toxicity.[221] Intragastric administration of capsaicin (50 mg kg^{-1} day^{-1}) or crude extract of capsicum (0.5 mg kg^{-1} day^{-1}) for 60 days was conducted in rats by Monsereenusorn.[257] The findings of Monsereenusorn are in concordance with those reported by Nopanitaya.[256] Biochemical parameters altered by capsaicin and crude extract included significant reductions in plasma urea nitrogen, glucose, phospholipids, triglyceride, transaminase and alkaline phosphatase.

Chlorobenzylidene malononitrile (CS). Repeated-dose studies with CS have been conducted in several species by inhalation and oral routes and the findings are reported.[258] Inhalation studies conducted on rats and dogs are highlighted. In these studies, animals were exposed for 4–5 min daily for 5 days/a week for 5 weeks to thermally-dispersed CS. The daily dosage of CS to the dogs was 680 mg·min m^{-3}, with a total accumulated dosage of 17 000 mg·min m^{-3}. For rats, the daily dosage of CS was 3640 mg·min m^{-3} with a total accumulated dosage of 91 000 mg·min m^{-3}. During the exposure, rats manifested a heightened degree of hyperactivity and aggressive behavior. In CS-exposed rats, accumulated dosages of 25 000 and 68 000 mg·min m^{-3} resulted in mortalities. Gross pathological changes were not 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. Marrs and co-workers[259] studied the effects of neat CS aerosol in rats, mice and guinea-pigs subjected to repeated inhalation doses (1 h day^{-1}, 5 days a week, for 120 days) of test article. High concentrations of CS were fatal to the animals after several exposures. Mortality in the low- and mid-dose animals was not significantly different from controls. It was concluded that CS concentrations <30 mg m^{-3} were without deleterious effects. These concentrations of CS are about ten times the intolerable level (3 mg m^{-3} for 1 min) estimated for humans.

Dibenz[b,f]1 : 4-oxazepine (CR).   Acute toxicity studies on CR have established the low toxicity of this substance and the absence of untoward effects involving altered morphology (i.e. respiratory tract lesions) and altered biochemical parameters (i.e. altered lung surfactant). Nevertheless, concerns over the health effects arising from multiple exposures to this class of chemicals have prompted a number of repeated-dose studies to evaluate clinicobiochemical, physiological and morphological parameters. Marrs and co-workers[260] reported findings on the repeated-dose inhalation toxicity of aerosolized CR (technical grade) in mice and hamsters. Animals were exposed to CR for up to 10 min at test article concentrations of 204, 236 and 267 mg m^{-3} for 5 days a week for 18 weeks. Follow-up observations on animals retained for up to 1 year after the start of the exposure were conducted to detect recovery from or persistence of toxic effects. High concentrations (mean daily Ct of 4222 mg·min m^{-3}) of CR affected the survival of both species and no single cause of death could be ascertained, although pneumonitis was evident in many cases. The CR exposure produced minimal organ toxicity; however, chronic inflammation of the larynx was noted in mice—findings consistent with repeated-dose exposure to irritants. No significant pulmonary lesions were manifest. In contrast to the aforementioned findings, no lung tumors were noted in hamsters exposed to CR. Likewise, no lesions were present in the larynx of hamsters exposed to CR aerosol. Histopathological evaluation of the liver revealed hepatic lesions in mice; however, these were of infective origin and not test article related. Based on their findings, Marrs et al.[260] concluded that exposure to high concentrations of CR reduced survivability, and that CR produced minimal organ-specific toxicity at levels many times ($\sim$200$\times$) the intolerable human dose (IC$_{50}$ = 0.7 mg m^{-3} within 1 min;[29] IC$_{50}$ = 0.15 mg m^{-3} within 1 min.[261] Kumar et al.[262] performed a toxicological evaluation of CR after repeated inhalation exposure in mice. Mice were subjected to 15-min daily inhalation exposures of CR at a concentration of 1008 mg m^{-3} for 5 and 10 days, a level equivalent to the 0.05 LC$_{50}$ dose. Biochemical parameters evaluated were hepatic lipid peroxidation (malondialdehyde (MDA) formation), glutathione (GSH) levels, liver acid phosphatase (ACP), liver alkaline phosphatase (ALP), glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT). The liver, lungs and kidneys were evaluated for histopathological changes. Significant decreases in body weight gain were noted in animals exposed to CR.

Hepatic biochemical parameters were not altered significantly by exposure to CR. Histopathological changes were noted in CR-exposed animals: mild congestion and intra-alveolar hemorrhages (focal in nature) of pulmonary tissue. The severity of these lesions increased with the number of exposures. Overall, these findings were consistent with results reported by Ballantyne,[71] who examined the cumulative 5-day oral toxicity of CR in various animals.

A number of studies have been reported on the repeated-dose toxicity of CR following dermal administration.[51,54,263] Owens and co-workers[51] studied the effects of CR in rabbits and monkeys following cutaneous application of test article applied daily for 5 days; however, assessment was limited to dermal effects only. In the study by Marrs and co-workers,[263] CR in acetone was applied to the skin of mice (C3H and Porton strains) for 5 days a week for up to 12 weeks. Two control groups consisted of the solvent group and untreated controls. Animals were kept for an additional 80 weeks following the end of the application period. In general, a greater degree of histological abnormalities was noted in the Porton strain of mice than that observed in the C3H strain of mice. 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, most likely due to acetone. It was concluded that the repeated dermal application of CR had little effect on the skin. The authors further postulated that in view of the absence of any specific organ toxicity the absorption of even substantial amounts of CR would have little effect.

Chloroacetophenone (CN).   McNamara et al.[61] summarized the findings of a repeated-dose inhalation study on the effects of thermally generated CN on monkeys, dogs and guinea-pigs. In one set of experiments, monkeys and guinea pigs were exposed for ten consecutive days to CN at Cts between 2300–4000 mg·min m^{-3} for a total exposure dosage of 31 445 mg·min m^{-3}. This dosage is considered lethal to $\sim$75% of the guinea pigs and 100% lethal to monkeys if given in a single exposure. Exposure to CN for 10 days resulted in the death of five guinea pigs; however, no deaths occurred in monkeys subjected to multiple exposures of CN. The data suggest that the toxicity of CN is considerably less when administered in divided dosages. In another multiple inhalation exposure study involving CN, also summarized by McNamara et al.[61] dogs were exposed on ten consecutive days to CN at Cts ranging between 3000–7000 mg·min m^{-3} for a total dosage of 60 000 mg·min m^{-3}. A subsequent repeated-dose inhalation study also was conducted in guinea-pigs, dogs and monkeys exposed daily for 10 days to Cts between 4200–13 000 mg·min m^{-3} for a total exposure of 88 000 mg·min m^{-3}. This dosage was determined to be lethal in the majority of animals for all species tested. Collectively, these studies demonstrated the lack of cumulative toxicity of CN when administered as repeat doses. In a recent study, Kumar and co-workers[262] reported findings on the effects of multiple exposure to CN and CR in mice. Animals were exposed to test article at concentrations equivalent to the 0.05 LC$_{50}$ (87 mg m^{-3} of CN) for 15 min a day for 5 and 10 days. Biochemical endpoints measured included blood glucose, plasma urea, liver alkaline phosphatase (ALP), liver acid phosphatase (ACP),

transaminase enzymes (SGOT, SGPT), liver glutathione (GSH) levels and hepatic lipid peroxidation (malondialdehyde (MDA) formation). Histological evaluation of pulmonary, hepatic and renal tissues also was performed. Clinical parameters affected following repeated exposure to CN were characterized as hepatic glutathione depletion, increased lipid peroxidation and increased hepatic acid phosphatase activity. The CN-induced elevation in acid phosphatase levels reflected the release of lysosomal enzyme from the liver, indicative of tissue injury. Additionally, hyperglycemia was observed after exposure to CN, an effect previously reported by Husain *et al.*[264] It was postulated that hyperglycemia may have been induced by stress-mediated release of epinephrine, which is known to elevate glucose levels. Significant decreases in body weight gain also were noted on exposure to these compounds, with CN having a more prominent effect on body weight. Histopathological changes of the lung 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 centrolobular necrosis of hepatocytes following CN exposure. The National Institutes of Health cited a subchronic study on CN that was conducted under the National Toxicology Program.[265] 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.

Reproductive/developmental toxicity

Upshall[266] studied the developmental toxicity of CS in rats and rabbits exposed via inhalation to test article at a concentration of $\sim$10 mg m^{-3}, which represents the level most likely to exist in riot control situations. Fetuses were examined for abnormalities and no increase of significance was noted in the numbers of abnormal fetuses or resorptions. But it should be acknowledged that the exposure conditions (low dosages and short exposure duration of $\sim$5 min) may not have been adequate to assess the fetotoxic and teratogenic potential of CS. Teratology studies are conducted routinely at dosages that produce maternal toxicity. No data were presented regarding the degree of maternal toxicity or mortality. 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.

The effects of CR on rabbit and rat embryonic development were studied by Upshall.[267] Animals were exposed to aerosolized CR at concentrations of 2, 20 and 200 mg m^{-3} for 5- to 7-min exposures. The highest concentration represents a level about 200 times the intolerable concentration of CR to humans. Additionally, some rats were dosed intragastrically at 2, 20 and 100 mg kg^{-1} on days 6, 8, 10,12, and 14 of pregnancy and others were dosed intragastrically with 400 mg kg^{-1} on days 7, 10 and 13 of pregnancy. Rabbits were dosed intragastrically with CR (0.2, 2 and 20 mg kg^{-1}) 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. Although

the concentration of CR aerosol represented a level much higher than the concentrations expected under riot control situations (i.e. 10 mg m^{-3}), 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. Based on the overall observations, the authors concluded that CR was neither teratogenic nor embryotoxic to rats and rabbits.

Genotoxicity and carcinogenicity

Capsaicin and capsaicinoids. There is widespread concern regarding the mutagenic and carcinogenic potential of capsaicinoids, because these substances are metabolized to derivatives with the capability of alkylating genetic material. Thus, the mutagenic potential of capsaicinoids has been studied in both microbial and mammalian genotoxicity assays. The mutagenicity of capsaicinoids has been tested extensively in the Ames (*S. typhimurium*) assay.[268-272] Buchanan and co-workers[268] evaluated the mutagenicity of chilli pepper oleoresins and capsaicinoids, and neither the oleoresin nor the purified capsaicin produced mutations in *S. typhimurium*. In studies by Toth and co-workers,[269] purified capsaicinoids exhibited mutagenic activity in the presence of liver-activating enzymes. Damhoeri and co-workers[270] studied the mutagenic potential of capsicum pepper (oleoresins) using *S. typhimurium* in the absence of metabolic activation. Under the conditions of the assay, the oleoresins were found to be mutagenic. Nagabhushan and Bhide,[271] in assessing the mutagenicity of capsaicin in *S. typhimurium* strains, reported that capsaicin was mutagenic with metabolic activation. In genotoxicity studies by Gannett *et al.*,[272] 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. The findings of Gannett and co-workers suggest that capsaicin and the pepper extract were not genotoxic. In the rec^{+}/rec^{-} assay, capsaicinoids were non-mutagenic for *B. subtilis*.[273] The mutagenic potential of capsaicinoids also has been evaluated in bioassays using mammalian cells (i.e. V79 cell line) to ascertain the mutagenic potential for capsaicinoids.[271,272,274] In the V79 mammalian test system, Nagabhushan and Bhide[271] reported that capsaicin was non-mutagenic. However, studies by Gannett *et al.*[272] and Lawson and Gannett[274] using the V79 cell line suggested that capsaicin and capsaicinoids were genotoxic. Using the Micronucleus Mutation Assay, Naghabhushan and Bhide[271] evaluated the mutagenic potential of capsaicin. Results from these studies indicated that capsaicin was positive for mutagenicity. The mutagenic potential of capsaicin was assessed also in the Dominant Lethal Assay by Narasimhamurthy and Narasimhamurthy.[275] Capsaicin was found not to be mutagenic in this bioassay. In spite of equivocal findings regarding the mutagenic potential of capsaicin and capsaicinoids, the prudent approach from

the health hazard perspective is that these compounds should be regarded as having genotoxic potential.

In human populations who routinely use peppers in their diet, an increased incidence of gastric cancer is noted.[276–278] Capsaicin has been reported to induce mucous fibrosis in the oral cavity and could be relevant in the development of esophageal cancer.[279,280] When administered in the diet, capsaicin induced cancer in the mouse duodenum.[269] Studies by Kim et al.[281] suggest that capsaicinoids may act as co-carcinogens. A rodent carcinogenesis bioassay to assess the carcinogenic potential of capsaicin was conducted by Toth and Gannet.[282] 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 studied by LaHann[283] and Sasajima et al.[284] LaHann[283] concluded that capsaicin appeared to facilitate the onset of TPA-induced tumor formation and that capsaicin could enhance the risk of skin cancer. Studies by Sasajima and co-workers[284] demonstrated that capsaicin induced ornithine decarboxylase (ODC) activity, an enzyme used as an index of tumor-promoting capability. Based on the collective data, there appears to be sufficient evidence that capsaicin may pose a tumorigenic threat.

Chlorobenzylidene malonoritile (CS).   The mutagenic potentials of CS and CS2, a formulation containing CS in a mixture of 5% Cab-o-Sil® and 1% methyldisilizane, have been studied in microbial and mammalian bioassays. As reported by von Daniken et al.,[285] CS was positive for mutagenicity in the Ames assay; however, subsequent findings by Zeiger et al.[286] indicated questionable genotoxicity for S. typhimurium. Findings by Rietveld et al.[287] and Wild et al.[288] indicated that CS was non-mutagenic for S. typhimurium. Mutagenicity studies by Meshram et al.[289] using the Ames assay also demonstrated that CS did not induce a mutagenic response in the presence or absence of S9 mix. CS2, a mixture of micropulverized CS and an aerogel, was negative when tested in S. typhimurium strains TA98, TA 1535 and TA 1537 with or without metabolic activation.[290] The genotoxic potentials of CS and CS2 were evaluated using various mammalian genotoxicity assays, which included 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.[290–292] The results of these assays indicated that CS2 induced sister chromatid exchanges, resulted in chromosomal abberations and caused induction of Tft resistance.

Carcinogenicity studies of CS2 were conducted in rats (F2344/N) and mice (B6C3F1).[290] Animals were exposed via inhalation over their lifetime to CS2 aerosol. Compound-related non-neoplastic lesions characterized as hyperplasia and squamous metaplasia of the respiratory epithelium and degenerative changes of the olfactory epithelium were evident in CS2-exposed rats. Pathological changes observed in CS2-exposed rats included squamous

metaplasia of the olfactory epithelium as well as hyperplasia and metaplasia of the respiratory epithelium. Hyperplasia and squamous metaplasia of the respiratory epithelium were noted also in mice exposed to CS2. These findings are not unexpected because the epithelium of transitional areas of the respiratory tract is reported to be the most sensitive areas for cellular alterations such as epithelial degeneration, hyperplasia and squamous metaplasia following exposure to irritants.[293,294] 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.

Dibenz[b,f]1 : 4-oxazepine (CR).   There is a paucity of data addressing the subject of genotoxic potential of CR. A review of the database has identified a single study in the mainstream medical literature. Colgrave et al.[295] evaluated the mutagenic potential of CR and its precursor (2-aminodiphenyl ether) in microbial and mammalian genotoxicity bioassays. The S. typhimurium assay 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). Both CR and its precursor were negative in all assays. The results from such varied bioassays would suggest that CR does not pose a mutagenic threat; however, additional genotoxicity testing would establish CR as a non-mutagen. The carcinogenic potential of CR is unknown because very little research has been conducted to ascertain the ability of CR to produce neoplasia or long-term effects. However, Marrs and co-workers[263] in a repeated-dose (18 week) study have reported the occurrence of alveologenic carcinoma in a single low-dose group mouse and in a single high-dose group mouse. This tumor type was observed also in a control mouse. The validity of these findings, as well as interpretations/conclusions, may be questioned because the spontaneous frequency of alveologenic carcinoma is high in many mouse strains.[296,297] Further, this tumor type is dissimilar in many respects from human types of lung tumors.

Chloroacetophenone (CN).   Carcinogenicity bioassays have been conducted in rats and mice to ascertain the carcinogenic potential of 2-chloroacetophenone.[265] There was no indication of carcinogenic activity of CN in male rats exposed to test article. Equivocal evidence of carcinogenicity of CN 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.

Uptake, distribution, metabolism and excretion

Capsaicin and capsaicinoids.   Saria et al.[298] studied the distribution of capsaicin in tissues of rats following systemic administration. 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
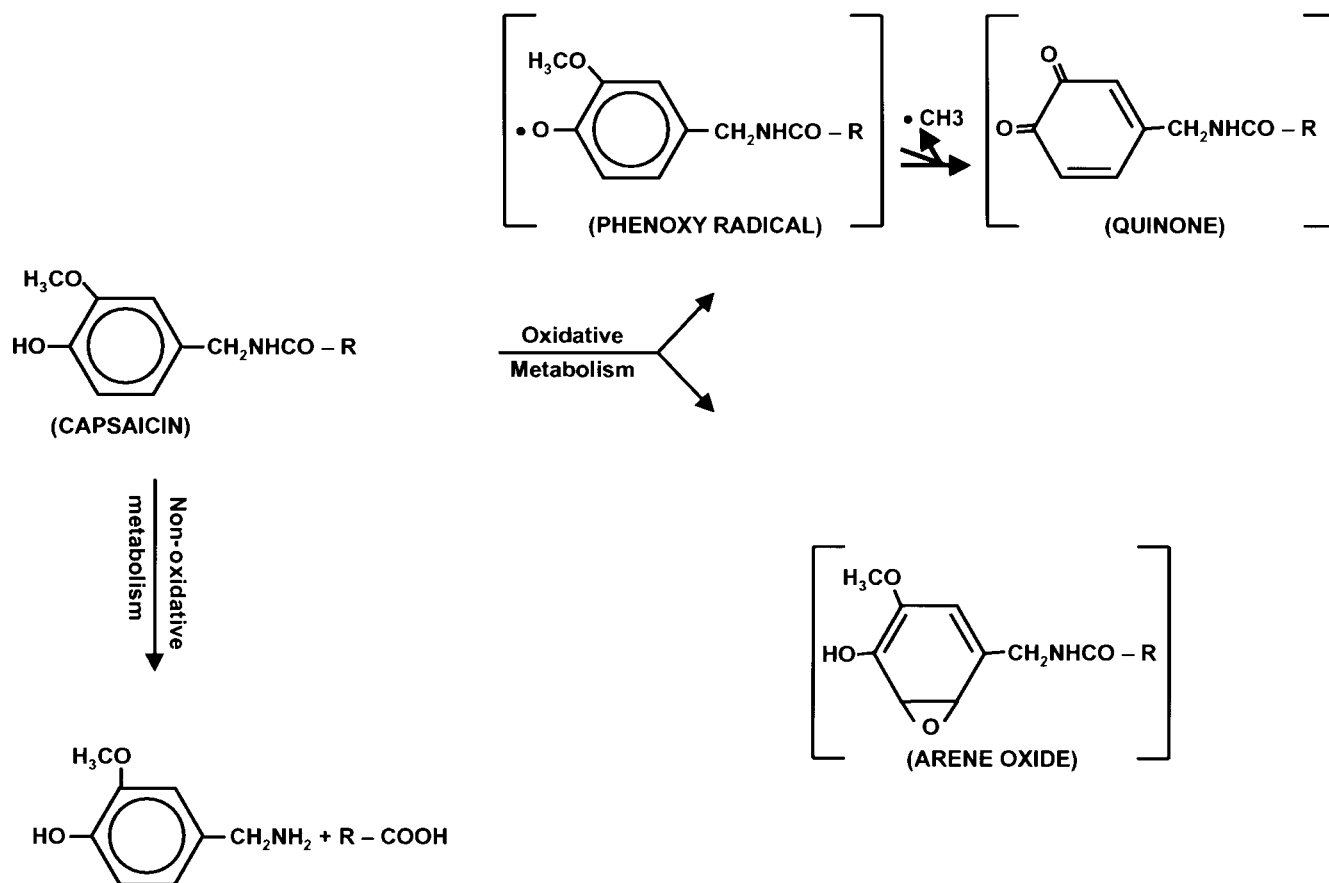
Figure 3. Capsaicin bioconversion pathways.

on s.c. administration; however, detectable levels of capsaicin were found in various tissues. Kim and Park[299] suggested that capsaicin and its analogs were poorly absorbed in the gut, which led Kawada et al.[300] to investigate further the gastrointestinal uptake of capsaicin and associated analogs conducted *in vivo* and *in situ* absorption studies in rats. Their findings indicated that absorption of capsaicin and dihydrocapsaicin occurred rapidly from the stomach and small intestine—~85% of the dose was absorbed from the gastrointestinal tract. Regional capacities for uptake also were investigated. Results indicated regional differences in the absorption of capsaicin from the gastrointestinal tract. The findings reported by Kawada et al.[300] are in agreement with the *in vitro* results reported by Monsereenusorn[301] regarding the *in vitro* intestinal absorption of capsaicin. The degree and processes of absorption of capsaicin and capsaicinoids in the respiratory tract have not been elucidated. 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). Kawada and Iwai[302] studied the *in vivo* and *in vitro* metabolism of the capsaicin analog dihydrocapsaicin in rats. 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 studied initially by Lee and Kumar.[303] They demonstrated the conversion to catechol metabolites via hydroxylation on the vanillyl ring moiety—findings later confirmed by Miller et al.[169] The conversion of capsaicin by the liver mixed-function oxidase system to an electrophilic epoxide is one example of metabolism to an electrophilic metabolite. Other pathways leading to highly reactive intermediates involve the formation of a phenoxy radical as well as the formation of a quinone-type product.[93] The generation of a quinone derivative is believed to proceed via O-demethylation at the aromatic ring with concomitant oxidation to the semiquinone and quinone derivatives or via demethylation of the phenoxy radical intermediate of capsaicin (see Fig. 3). It should be noted also that the quinone pathway involving the phenoxy radical leads to the formation of an extremely reactive methyl radical. In addition to the above oxidative pathways, the alkyl side chain of capsaicin is susceptible to enzymatic oxidation (oxidative deamination).[304] Capsaicin may also undergo non-oxidative metabolism via hydrolysis of the acid amide bond to yield vanillylamine and fatty acyl moieties (see Fig. 3).[300,302,305]

Chlorobenzylidene malonoritite (CS). Leadbeater[306] reported findings regarding the uptake of CS by the respiratory tract of animals and humans, the gastrointestinal absorption of CS in rats and its metabolic conversion. The absorption of CS from the respiratory tract is very rapid, and the half-lives of CS and its principal bioconversion products are reported to be extremely short.[306] The elimination of CS follows first-order kinetics over the dose range examined. It spontaneously hydrolyzes to malononitrile,[307] which is transformed to cyanide in animal tissues.[308,309] It undergoes metabolic

conversion to 2-chlorobenzyl malononitrile (CSH₂), 2-chlorobenzaldehyde (*o*CB), 2-chlorohippuric acid and thiocyanate.[29,242,306,310–312] Both CS and its metabolites can be detected in the blood following inhalation exposure, but only after large inhalation doses. Both CS and two of its metabolites 2-chlorobenzaldehyde and 2-chlorobenzyl malononitrile were detected in the blood following inhalation exposure of rodent and non-rodent species to CS aerosol.[306,311] Brewster and co-workers[313] studied the fate of CS in rats following intravenous and intragastric doses. Findings from these studies indicated that in most cases the majority of the administered dose was eliminated in the urine. A metabolic conversion that leads to a decrease in the lethal potency and peripheral sensory irritancy is the NADPH-dependent reduction of the benzylidene double bond in CS to yield 2-chlorobenzaldehyde (*o*-chlorobenzaldehyde). The *in vivo* conversion of CS to 2-chlorobenzaldehyde is followed by further bioconversion to the 2-chlorobenzoic acid intermediate, which undergoes subsequent glycine conjugation or reduction to 2-chlorobenzyl alcohol with ultimate excretion as 2-chlorobenzyl acetyl cysteine or 1-*O*-(2-chlorobenzyl) glucuronic acid (see Fig. 4). The principal urinary metabolites of CS are 2-chlorohippuric acid, 1-*O*-(2-chlorobenzyl) glucuronic acid, 2-chlorobenzyl cysteine and 2-chlorobenzoic acid.[310] Lesser amounts of 2-chlorophenyl acetyl glycine, 2-chlorobenzyl alcohol and 2-chlorophenyl 2-cyanopropionate also were identified. Leadbeater[306] also studied the uptake of CS by the human respiratory tract and found trace amounts of 2-chlorobenzyl malononitrile in the blood; however, CS and 2-chlorobenzaldehyde were not detected after exposure to a very high dose of CS ($Ct = 90$ mg·min m⁻³). These results are in concordance with CS uptake studies in animals and with the maximum tolerable concentration in humans, which is <10 mg m⁻³. Leadbeater theorized that significant amounts of CS would not be absorbed via inhalation at or near the tolerable concentration.

The formation of cyanide from CS has been the subject of several studies in laboratory animals and in humans.[242,306,314,315] Free cyanide has been detected following i.v. administration of CS in dogs exposed to lethal doses of CS, but little experimental data were presented.[242] It is of interest to note that CS and malononitrile possess two nitrile residues and in theory may give rise to two cyanide ions per molecule of the parent compound. Experiments were conducted to test this postulate, and data suggest that under *in vivo* conditions only one cyanide radical is converted to cyanide, thus the total amount of cyanide generated may be minimal.[29] Studies to ascertain cyanide production, measured as plasma thiocyanate levels in human subjects exposed to CS, have been conducted.[306,314] Findings from these studies have indicated negligible levels of plasma thiocyanate.

Dibenz[*b*,*f*]1 : 4-oxazepine (CR).

As part of the toxicological assessment of CR, the biotransformation and metabolic fate of CR have been studied in a number of animals.[316–321] Human metabolic studies on CR have not been conducted owing to the very high sensitivity of humans to the irritant properties of CR, which has precluded metabolic studies because the maximal tolerated dosage is too low to prevent metabolic detection. Aerosols of CR are rapidly absorbed from the
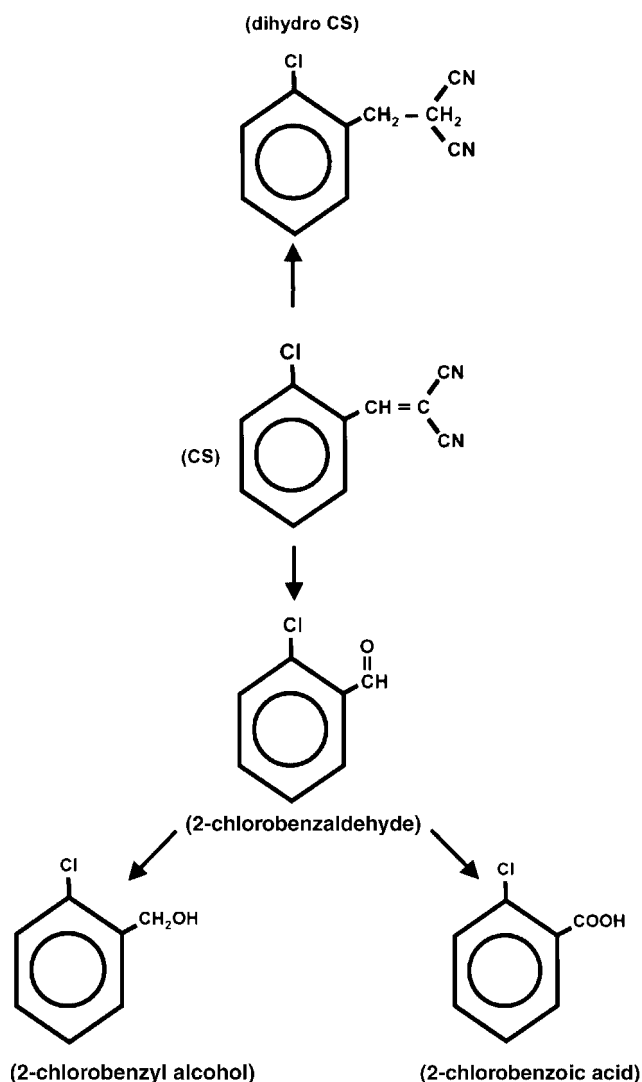
Figure 4. CS metabolic pathways.

respiratory tract, and the plasma half-life ($T_{1/2}$) of CR after inhalation exposure to CR aerosol is ~5 min. The plasma half-life of CR following i.v. administration is also ~5 min. The uptake and metabolic fate of CR in intact cornea and corneal homogenates was studied by Balfour.[317] The data indicated that these tissues readily took up CR and metabolized CR to a lactam derivative. French and co-workers[319,320] and Furnival *et al.*[321] have studied the metabolism and fate of CR in a series of *in vivo* and *in vitro* studies. French *et al.*[319] studied the *in vivo* metabolism and metabolic fate of CR in rats, guinea pigs and monkeys after intragastric dosing of CR and i.v. administration of CR to rats and mice. It was effectively absorbed from the gastrointestinal tract and the fate of absorbed CR was, in general, similar to that following i.v. administration. Similar excretory patterns and metabolites were noted among the species, with urinary excretion as the major route of elimination. In the rat, CR is converted to the lactam derivative followed by subsequent hydroxylation to monohydroxylated derivatives (i.e. 4-,7- and 9-hydroxylactams) and the eventual formation of sulfate conjugates (see Fig. 5). In the rat, the major conjugation pathway for CR metabolic products involves sulfate conjugation, which is irrespective of dose and the route of administration. The bile contained
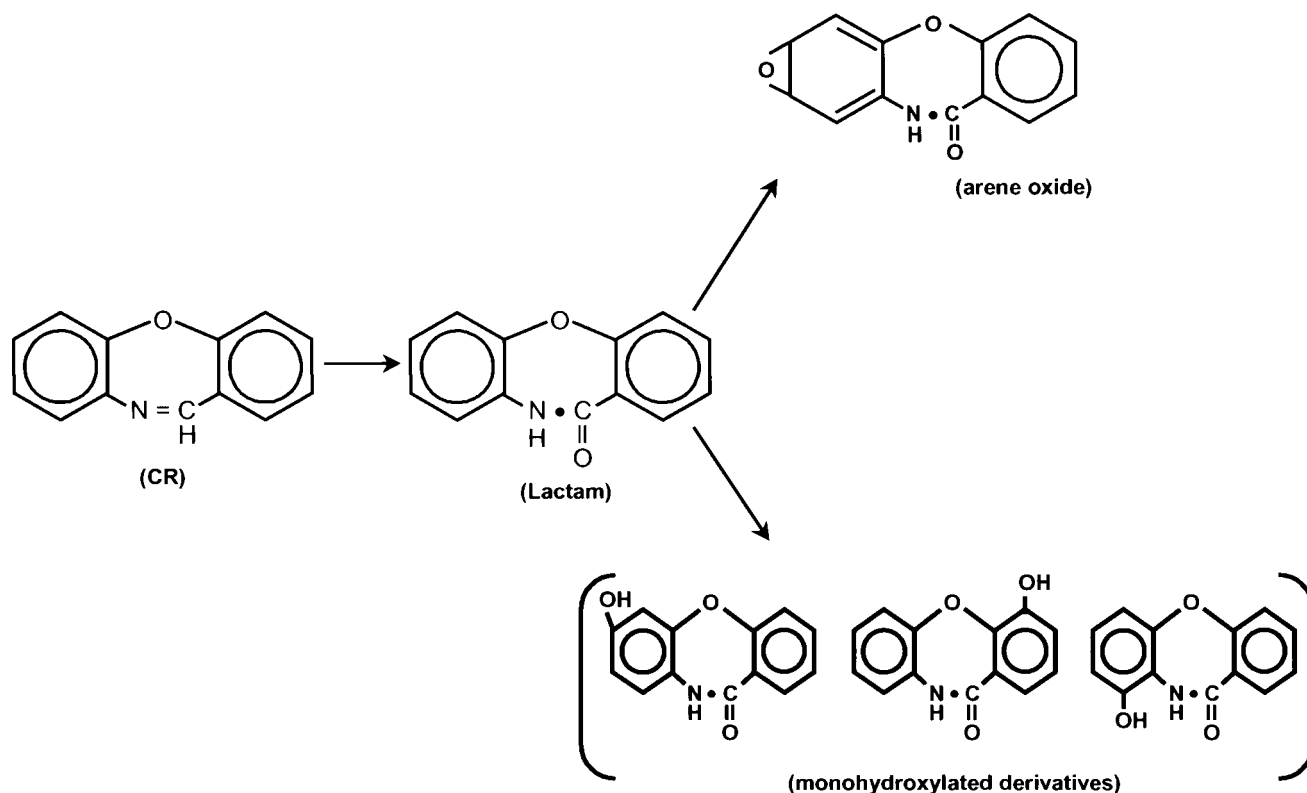
Figure 5. Bioconversion pathways for CR.

only small levels of sulfate conjugates. In his review on the metabolism of CR, Upshall[316] had also discussed glucuronide conjugate formation involving CR metabolic intermediates as an additional conjugation pathway, which are eventually excreted in the urine as sulfate conjugates. French and co-workers[319] point out that similar metabolic products and excretory pathways exist; however, only free hydroxylactams were isolated from monkey urine. In the same study,[319] whole-body autoradiography studies were performed in i.v.-dosed mice and the results suggested the rapid uptake of CR from the blood into other compartments such as the liver, kidney and small intestine. These findings are consistent with rat studies indicating rapid absorption, hepatic metabolism, biliary secretion, interohepatic recirculation and renal excretion. *In vitro* metabolic studies that utilized rat liver preparations were conducted by Furnival and co-workers.[321] The findings demonstrated that CR metabolic conversion involved ring opening and reduction and oxidation to lactams. Additional *in vitro* and *in vivo* metabolic studies were conducted by French *et al.*[320] Results from these studies supported previous conclusions that the major metabolic fate of CR in the rat is oxidation to the lactam, subsequent ring hydroxylation, sulfate conjugation and urinary excretion. With the exception of CR-lactam, phase I metabolites of CR are acutely less toxic than the parent compound.[319]

Chloroacetophenone (CN). The metabolism and full metabolic fate of CN have not been studied in great detail and are poorly characterized. What is known concerning the metabolism of CN is that it is converted to an electrophilic metabolite. It is an SN_2 alkylating agent that reacts with SH groups and nucleophilic sites of macromolecules. Alkylation of SH-containing enzymes leads to enzyme inactivation with subsequent disruption of cellular processes. Based on the potential to disrupt enzyme function, Castro[322] examined the effects of various alkylating agents, including CN, on human plasma cholinesterase. Chloroacetophenone inhibited ChE activity but not as a consequence of interaction with SH moieties. It is postulated that some of the toxic actions of CN may be due to alkylation of SH-containing enzymes.

Mechanisms, interactions and cytotoxicity

The mechanism(s) underlying the pharmacological/physiological effects and the mechanism(s) responsible for the toxic effects of riot control agents are reviewed. The underlying mechanism(s) of action of some of the riot control agents, such as capsaicin, is better understood and more fully delineated than it is for other riot control agents such as CR. A great portion of the discussion related to mechanisms of action focuses on the adverse effects, whose etiology stems from the interaction of toxic electrophilic metabolites of riot control agents that alkylate critical molecular targets such as DNA and proteins. Interactions of electrophilic metabolites with nucleophilic moieties of biological material with potential consequences are highlighted in Fig. 6. Discussion also includes the generation of other toxic metabolic products of riot control agents, such as reactive oxygen species (ROS) and cytotoxic metabolites such as cyanide and their interactions with biochemical and physiological processes, which lead to deleterious effects. Adverse effects that may result from such toxic metabolites include mutagenesis, carcinogenesis, immunotoxicity, perturbations involving bioenergetic pathways, oxidation of macromolecules (i.e. DNA, proteins and lipids), alteration of detoxication
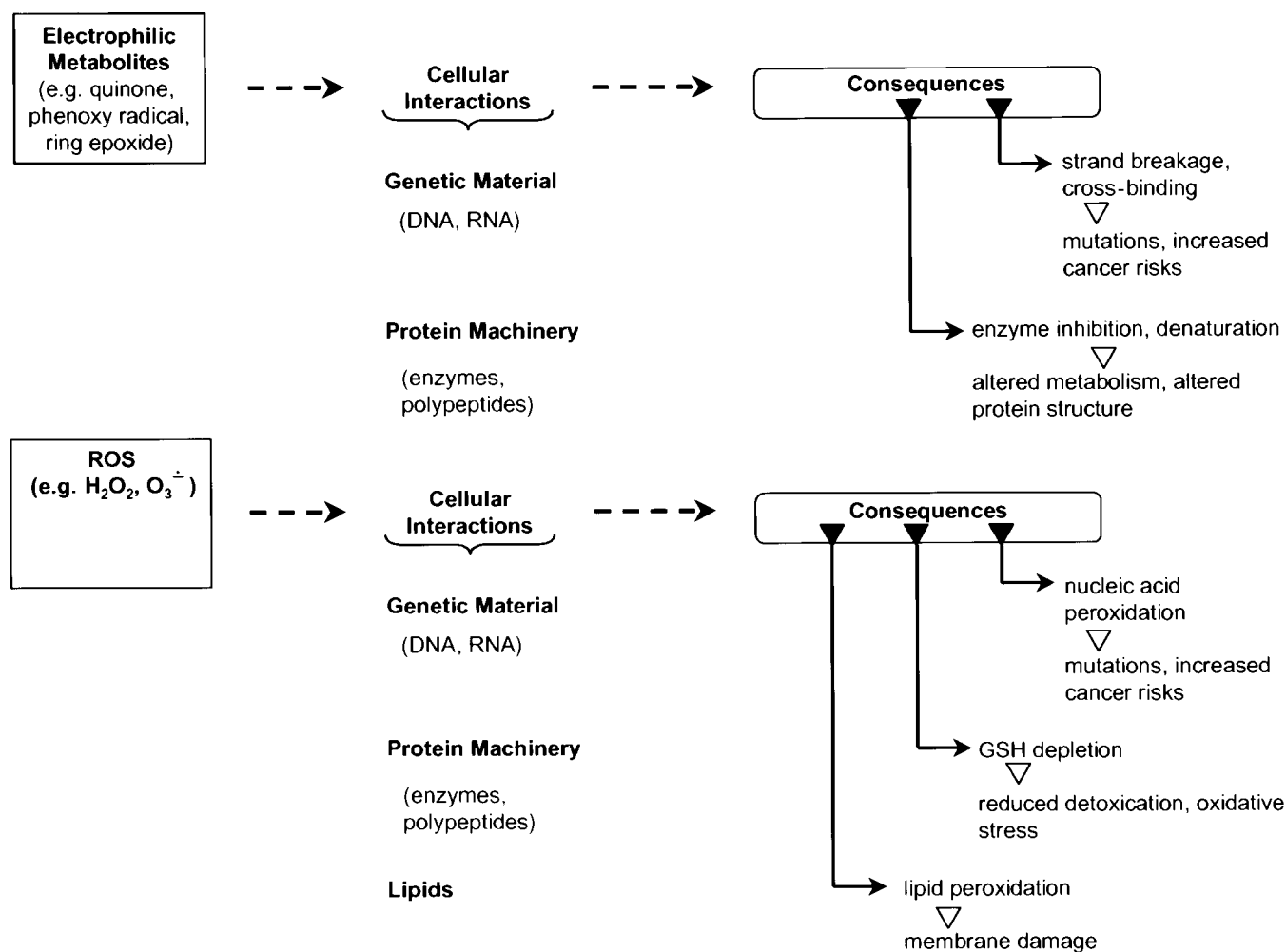
Figure 6. Biological interactions of toxic metabolites with nucleophilic moieties and there consequences.

processes/capabilities, cytotoxicity and the activation of signaling pathways involved in pathological processes and carcinogenesis. The mechanisms by which some of these toxic intermediates (e.g. phenoxy radicals, quinones, $^{\bullet}CH_3$ and ROS) can produce adverse effects may be straightforward, or rather complex as in the case of toxic intermediates such as quinones.

Capsaicin and capsaicinoids. It is important to determine whether a single mechanism of neurotoxicity accounts for capsaicin-induced degeneration in the diverse population of capsaicin-sensitive neurons in the peripheral and central nervous system.[323–326] It is now well accepted that the specific action of capsaicin on a subpopulation of neuropeptide-containing afferent neurons involves the activation of a specific receptor that recognizes capsaicin/capsaicin-like compounds (the 'vanilloid' receptor).[327–330] This leads to the opening of a peculiar type of receptor-operated cation channel.[325,331] The consequent influx of Ca and Na leads to depolarization, triggering the local release of neuropeptides, central protective reflexes and autonomic motor responses.[197,332,333] A transient excitation of primary afferents is followed by a more prolonged condition of refractoriness whereby the primary afferents become unresponsive to further application of capsaicin /capsaicin-like agents—densensitization of the primary afferent neuron. The excitotoxic actions of capsaicin

is the result of calcium and sodium influxes via a capsaicin-activated channel.[325,331] The influx of Ca and Na may cause rapid damage and eventual cell death by osmosis and calcium-dependent proteases.[334] The ionic mechanisms underlying the actions of capsaicin on primary afferent neurons have been established.[324,325] When capsaicin is administered s.c. at 50 mg kg^{-1} to neonatal rats, >50% of the dorsal root ganglion (DRG) neurons are rapidly destroyed.[110,183]

The acute biological effects of capsaicin are due to the release of bioactive compounds (e.g., substance P, neurokinin A and calcitonin gene-related peptide (CGRP)) from sensory nerves by capsaicin, resulting in altered neurophysiology of sensory neurons in the airway mucosa and neuromediated inflammation of the epithelium, airway blood vessels, glands and smooth muscle, which leads to bronchoconstriction, mucous secretion, edema of the tracheobronchial mucosa, enhanced vascular permeability and neutrophil chemotaxis.[176,186,335–344] Biochemical and histochemical markers associated with primary afferent neurons include a number of peptides such as substance P, somatostatin, neurotensin and calcitonin gene-related peptide. These bioactive materials play a role in the communication of primary sensory neurons with other neural and non-neural cells.[345,346] The mechanisms—e.g. the release of neuropeptides (substance P, neurokinin A), involvement of CGRP and the induction

of ion fluxes in neurons—that underlie the pharmacological actions of capsaicin have been elucidated in part in the 1970s and 1980s.[84,111,112,132,150,192,347–357] Some of these effects, such as bronchoconstriction, vasodilatation and protein extravasation, are mediated by substance P, which belongs to a group of biologically active peptides referred to as tachykinins—the reader is referred to papers on substance P by Stern,[358] Leeman and Mroz,[359] Hokfelt et al.[360] and Lembeck and Gamse.[361] Substance P is one of the more thoroughly studied of these putative neurotransmitters. It was originally discovered by von Euler and Gaddum[362] and has been researched since the 1930s.[363] The isolation and biochemical characterization of substance P was reported by Chang and Leeman[364] and subsequently sequenced by Chang and colleagues.[365] Substance P is thought to have a neurotransmitter role in primary sensory neurons for central transmission of afferent information[366–368] and as a peripheral mediator of neurogenic inflammation and smooth-muscle contraction.[159,361,369] The aforementioned effects (bronchoconstriction, vasodilatation and plasma extravasation) are mimicked by substance P and/or inhibited by SP antagonists; however, other biological actions of capsaicin, e.g. the chronotropic and inotropic effect on the heart, are not mediated via substance P. As mentioned, 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 also may cause reflex bronchoconstriction by stimulating C fibers in both the pulmonary and bronchial circulation. Therefore, bronchoconstriction could be secondary to substance P release or to a vagal reflex.

In the previous section, discussion focused on the mechanisms that formed the basis for the neurotoxic action of capsaicin. Subsequent discussion on the mechanisms continues with a focus on the toxic metabolic products of capsaicin and their effects on the biological system. Surh and Lee[93] in their review on the metabolism and toxicity of capsaicin have discussed the role of metabolic activation in capsaicin-induced toxicity and the metabolic pathways involved in the bioconversion of capsaicin to electrophilic metabolites and other reactive moieties (e.g. ring epoxide, phenoxy radical and quinone). However, the interactions of these toxic metabolites with critical molecular targets and the consequences of such interactions were minimally addressed. In general, these moieties can interact with nucleophilic sites of macromolecules such as proteins, DNA and RNA that are thought to be critical in the etiology of capsaicin-induced cytotoxicity, mutagenicity and carcinogenicity. The formation of a quinone-type intermediate following metabolism of capsaicin is of great interest owing to the multiplicity of quinone-mediated effects, including alkylation of DNA and proteins, GSH depletion, reactive oxygen species (ROS) formation and ROS-related effects such as DNA oxidation and lipid peroxidation.

Quinones—activated metabolites of polycyclic aromatic hydrocarbons—represent a class of reactive intermediates that produce a number of deleterious effects, including cytotoxicity, immunotoxicity and carcinogenesis. The mechanisms by which quinones produce these effects can be via alkylation of proteins and/or DNA or by the formation of reactive oxygen species (ROS) that are generated by the redox cycling of quinones. Quinones

can react with nucleophilic amino groups of DNA and proteins. Additionally, quinones react with sulfur nucleophiles (i.e. GSH and cysteine residues of proteins), leading to protein alkylation and/or GSH depletion. The generation of ROS leads to severe oxidative stress in cells via the formation of oxidized cellular macromolecules (e.g. DNA, proteins and lipids) as well as activation of signaling pathways involved in the initiation, promotion and progression of carcinogenesis. For more in-depth discussion on the subject of quinone chemistry and toxicology, the reader is referred to Monks et al.[370] and Bolton et al.[371]

The hepatic cytochrome P-450-catalyzed conversion of capsaicin to reactive species includes the conversion to semiquinone and quinone derivatives. Quinones is a general term for a class of compounds that are endogenous biochemicals, are found in natural products or are generated via metabolism of xenobiotics. The quinone intermediate of capsaicin also represents an ultimate electrophilic metabolite. This intermediate can be formed by one of the following metabolic pathways: initial O-demethylation of the 3-methoxy group on the vanillyl ring with concomitant oxidation to the semiquinone or *o-quinone* derivatives; or O-demethylation of the phenoxy radical intermediate of capsaicin. The latter pathway generates the extremely reactive methyl radical, which is well-known to alkylate nucleic acids and proteins. Quinone derivatives of xenobiotics elicit toxic effects *in vivo*, including cytotoxicity, carcinogenicity and immunotoxicity. Cellular damage can occur via alkylation of critical cellular proteins and/or DNA. In addition, it should be recognized that redox cycling of quinones generates adducts and the formation of reactive oxygen species (ROS). Production of reactive oxygen moieties can lead to severe oxidative stress in cells via the formation of oxidized cellular macromolecules.

The alkylation of proteins and/or GSH by electrophilic metabolites of capsaicin has consequences affecting cellular energetics, detoxication processes, etc. The potential of covalent binding with microsomal protein, for example, may account for the impact of capsaicin on xenobiotic metabolizing enzymes and liver toxicity. In addition to the potential adverse reactions resulting from the interactions of cellular constituents with the metabolic products of capsaicin, deleterious effects result as a direct action of capsaicin on cellular processes, namely, cell bioenergetics. Concerning mitochondrial energy metabolism, Yagi[372] postulated that capsaicin and dihydrocapsaicin produce repression of NADH–quinone oxidoreductase activity, which confirms findings suggesting capsaicin-induced inhibitory effects on hepatic mitochondrial bioenergetics.

Chlorobenzylidene malononitrile (CS). The cyanogenic properties of CS have been investigated since Patai and Rappoport[307] demonstrated the hydrolysis of CS to malononitrile, the latter being converted to cyanide in animal tissues.[308,309] The conversion of CS to cyanide with malononitrile as an intermediate led Jones and Israel[373] to postulate that some of the toxic effects attributed to CS may arise from the conversion of CS *in vivo* to cyanide. It is understandable that considerable interest has evolved regarding the cyanogenic properties of CS because cyanide is an extremely toxic poison. The mechanism of action of cyanide is generally accepted as impairment of cellular respiration via the inhibition of cytochrome oxidase, leading to altered cellular electron

Table 9—Biochemical interactions and potential mechanisms of cellular injury involving CS

Interaction with biochemical constituent	Result	Biochemical system affected	Adverse toxicological consequences
Alkylation of glutathione (GSH)	GSH depletion	GSH peroxidase	Hydroperoxide build-up leading to oxidative damage and metabolic dysfunction (e.g. lipid peroxidation resulting in functional impairment of mitochondria; nucleic acid oxidation leading to mutations; hemoglobin oxidation resulting in diminished oxygen transport)
		GSH S-transferase	Decreased detoxification and excretion of harmful electrophilic metabolites via mercapturic acid pathway
		Cysteine transport[a]	Altered protein synthesis
Alkylation of SH-containing enzymes or biomolecules	Inactivation	Lactic dehydrogenase	Perturbed glycolysis; altered bioenergetics
	Lipoic acid[b] depletion	Pyruvate decarboxylase system	Decreased acetyl CoA resulting in perturbed cell bioenergetics and decreased lipogenesis
Alkylation of proteins	Inactivation	Various targets	Modified protein structure; non-specific cytotoxicity; cell death
Alkylation of nucleic acids	Inactivation	Nucleic acids	Mutations; alteration of genetic integrity

[a] Glutathione serves as a transport form of cysteine.
[b] Alkylation of dihydrolipoic acid, which is the disulfhydryl form of lipoic acid, is a coenzyme in the pyruvate decarboxylase system.

transport and resulting in cytotoxic hypoxia. Additionally, Way[374] has suggested that our understanding of the mechanistic aspects of cyanide–induced toxicity proceed beyond cytochrome oxidase inhibition to include also the following biochemical lesions: cyanide release of endogenous opioids, which may cause respiratory paralysis;[375,376] lipid peroxidation;[377,378] altered calcium levels;[379] and phospholipid hydrolysis.[380] Involvement of the aforementioned biochemical lesions in cyanide toxicity helps to explain the diverse biological effects of cyanide.

Maehly and Swensson[381] had conducted studies to ascertain urinary and blood levels of cyanide and thiocyanate in workers exposed to low levels of cyanide. With regard to the cyanogenic properties of CS, Frankenberg and Sorbo[315] conducted studies in animals to determine blood cyanide levels and thiocyanate excretion, as well as defining the relationship between cyanide levels and symptomatology. They determined blood cyanide levels and thiocyanate excretion in mice after intraperitoneal administration and inhalation exposure to CS. Mice were exposed to a CS aerosol dosage of 20 000 mg·min m^{-3}, which corresponded to about one-half of the LD_{50} for CS. This dosage resulted in high levels of blood cyanide that were reached rapidly, with peak levels 4–16 min after injection. Equitoxic doses of malononitrile and cyanide also were evaluated for generating blood cyanide.

Based in part on xenobiotic interactions with sulfhydryl groups[382] and the findings of Mackworth[383] and Dixon[384] on the inhibitory effect of various lacrimatory compounds on thiol enzymes, Lovre and Cucinell[385] and Cucinell et al.[242] studied the effects of the riot control agents CN and CR on SH-dependent enzyme systems. Lovre and Cucinell[385] postulated that sulfhydryl-containing enzymes

(e.g. lactic dehydrogenase, glutamic dehydrogenase and pyruvic decarboxylase) are alkylated by CS. Ballantyne and Swanston[238] also have reported that both CS and CN are SN_2 alkylating agents, indicating that they react directly with nucleophilic sites. Findings by Cucinell et al.[242] suggest that lactic dehydrogenase (LDH) is inhibited by CS, and enzyme inhibition via CS was partially reversed by the addition of excess glutathione (GSH) indicating the involvement of thiol groups. These findings led Cucinell et al.[242] to suggest that alkylation of nucleophilic sites, including SH containing enzymes, is the underlying biochemical lesion responsible for CS-induced toxicity. Chlorobenzylidene malononitrile is known to react with the SH groups of dihydrolipoic acid—the disulfhydryl form of lipoic acid—which is a coenzyme in the pyruvate decarboxylase system. Alteration of dihydrolipoic acid biochemistry can lead to decreased acetyl CoA levels, resulting in perturbation of cellular bioenergetics. The biochemical interactions and potential mechanisms of cellular injury involving CS are summarized in Table 9. Lastly, regarding the mechanism (s) of action of CS, it is theorized that the irritant and painful effect of CS may be due to bradykinin release.[81,242].

Clinical chemistry

Husain et al.[264] 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. 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

Table 10—Comparative toxicity of lacrimatory compounds: human estimates[1,2,4,6,12,17,19]

Compound	Minimal irritant conc. (mg · min m^{-3})	LCt_{50}[a] (mg · min m^{-3})	ICt_{50}[b] (mg · min m^{-3})
CN	0.3–1	8500–25 000	20–50
CR	0.002	>100 000	~1
CS	0.004	25 000–150 000	5
DM	1–5	11 000–35 000	20–150
Acrolein	2–7	3500–7000	—
Bromobenzyl cyanide	0.3	8000–11 000	30
Chloroacetone	18	>3000	—
Chloropicrin	2–9	2000	—
Xylyl bromide	~5	5600	—
Capsaicin	—	—	—

[a] LCt_{50}: the concentration × time (Ct) that is lethal to 50% of an exposed population.
[b] ICt_{50}: the concentration × time (Ct) that incapacitates 50% of an exposed population.

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. Conclusions drawn from the study was that exposure to CN aerosol could lead to tissue damage.

Human pharmacology and toxicology: clinical considerations related to riot control agent exposure

Riot control agents exert their effects on eyes, lungs and skin and can enter the body via the inhalation, dermal and oral routes of exposure. The clinical symptoms, which are felt within 10–30 s on exposure to riot control agents, are the consequence of these agents' ability to cause intense sensory irritation at various body sites. Almost immediately the eyes are affected, with copious lacrimation, blepharospasm, conjunctivitis and pain. Nasal effects consist of rhinorrhea, itching and pain; also, a stinging or burning sensation of the mucosal surfaces is experienced. Symptoms such as sneezing, coughing and increased respiratory tract secretions are accompanied by a burning sensation and chest tightness. The more severe effects identified as marked coughing, retching, and vomiting may occur if an individual remains in a riot control agent atmosphere. Psychological effects such as anxiety and panic are reactions that are commonly noted on exposure to these compounds. The intense physical discomfort and anxiety also can lead to cardiovascular changes such as increased blood pressure. Effects on the skin consist mainly of an intense burning sensation followed by erythema. After cessation of exposure, most symptoms persist for a brief period and by 30 min most symptoms have abated completely; however, 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 also may complicate and exacerbate existing conditions such as bronchitis and asthma. The comparative toxicity (human) of various lacrimatory compounds is summarized in Table 10.

Oleoresin capsicum (OC) and capsaicin. Oleoresin capsicum (OC, pepper spray), purportedly safe and effective, has seen increased adoption and utilization by law

enforcement agencies. Recently, Smith and Stopford[386] have reviewed the effects of exposure to OC sprays and have discussed the occupational health risks. Onnen,[387] on the subject of oleoresin capsicum as related to law enforcement, cited findings by Weaver and Jett[388] who reported the lack of adverse effects in humans exposed to OC. Recently, a number of reports have appeared pertaining to in-custody deaths and pepper spray use.[389,390] Granfield and colleagues[389] have published the findings of their review of aggregated data related to in-custody deaths where pepper spray was used. Thirty in-custody cases were reviewed to ascertain the role of pepper spray as being unrelated, contributory or causative. They concluded that OC had not contributed to or was the cause of death in 22 cases where sufficient information permitted a thorough review. Granfield *et al.* also discussed factors/conditions, e.g. positional asphyxia, cocaine intoxication, excited delirium (cocaine-induced) and neuroleptic malignant syndrome (NMS). In-custody deaths following OC (pepper spray) use also was the subject of a paper by Steffee *et al.*[390] They described two cases of in-custody death, both associated with the use of pepper spray. A detailed autopsy and toxicological analysis was performed, coupled with pre-mortem chain of events, symptomatology and degree of natural disease processes. Findings in the first case indicated that pepper spray neither caused nor contributed to the death, whereas in the second case the findings suggested a direct contribution of pepper spray to the death. The reader is referred to an excellent paper by Lifschultz and Donaghue[391] on the broader issues related to in-custody deaths. Of considerable interest concerning the potential life-threating and ill effects of OC is a report by Billmire *et al.*,[392] which describes the adverse health consequences of OC spray in an infant. In that incident, a 4-week-old healthy infant was exposed to 5% pepper gas when a self-defense device was accidentally discharged. The subject experienced respiratory failure and hypoxemia. The treatment regimen included extracorporeal membrane oxygenation. The patient was discharged and a subsequent 12-month follow-up was conducted that revealed several episodes of viral respiratory infections.

Studies have been published concerning the human response to inhaled capsaicin.[187,393–399] The human pharmacology of capsaicin has been reviewed by Fuller,[88] and Watson *et al.*[400] described the clinical effects in individuals

exposed to OC. The probable lethal oral dose of capsaicin for humans is considered to be 0.5–5.0 g kg^{-1}.[401] The upper respiratory tract effects on exposure to capsaicin have been described.[397,402] Healthy young human adult subjects that were challenged intranasally with capsaicin manifested rhinorrhea, sneezing, nasal burning and congestion.[397] Capsaicin application to the nasal mucosa produced a painful sensation and copious secretion of nasal fluid,[402] and these effects undergo desensitization after repeated application. Studies by Geppetti et al.[402] 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.

The larynx may represent the primary site of stimulation of inhaled capsaicin.[403] Because respiratory impairment is one of the most obvious effects observed in capsaicin-exposed animals, bronchoconstriction has been the subject of a number of human studies on capsaicin.[187,189,351,398] Fuller and co-workers[187] demonstrated that when inhaled in humans capsaicin produced a dose-dependent bronchoconstriction that was the same as in asthmatics and smokers. The majority of subjects manifested coughing and all reported retrosternal discomfort. The studies by Fuller and colleagues[187,398] confirmed that the bronchoconstrictor reflex following capsaicin stimulation in animals is present also in humans. The capsaicin-induced bronchoconstriction and the release of substance P—the putative neurotransmitter/neurogenic mediator found in sensory neurons—is 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.

Chlorobenzylidene malononitrile (CS).   On exposure to CS, humans manifest immediate signs and symptoms that disappear in minutes on cessation of exposure. Chlorobenzylidene malononitrile 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 ICt_{50} value, defined as the concentration that will incapacitate 50% of the exposed population in 1 min. The incapacitating signs and symptoms included intense burning of the eyes, profuse lacrimation, blepharospasm, burning sensation of the nose and respiratory tract, excessive salivation, tightness in the chest and a feeling of suffocation.[61] The time to incapacitation did not appear to differ among the test subjects exposed to CS via the different dispersion techniques, reduced ambient temperatures and subjects with medical histories suggestive of 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.[61] reported that people 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. Thus, it appears that adaptation develops gradually as the CS concentration increases. When the 'tolerant' individual left the contaminated area for short periods of 10–30 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.[234] Except for skin effects, workers in a CS manufacturing facility had not manifested untoward illness. Further, the mortality rate among these workers was less compared to other groups of men of the same age range.[404]

As the standard riot control agent of the US Army since 1959, CS has largely replaced CN as the riot control agent of choice worldwide. The selection of CS as the riot agent of choice was based on its low mammalian toxicity and high sensory irritant potency. It was used in the United Kingdom in 1969 to quell riots in Northern Ireland. Rose and Smith[26] have reported alleged toxic reactions in human beings exposed to agent CS, and reactive airway dysfunction (RADS) following exposure to CS was reported by Hu and Christiani.[405] The Himsworth Report (parts I and II)[404,406] was the focus of an in-depth inquiry into the adverse health and toxicological effects of CS following the use of CS in Londonderry, Northern Ireland, in 1969. There was no evidence of incapacitation that prevented an individual's egress from a CS-contaminated environment, even among the most heavily exposed individuals. Additionally, no evidence was found that previously healthy persons exposed 3 weeks before had developed any illness. Attention focused on susceptible subpopulations, namely, the very young, the elderly, 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. Regarding adverse effects on reproductive function and pregnancy, the Himsworth Committee[404] concluded that CS exposure had not significantly affected reproductive physiology; however, meaningful epidemiological studies were not conducted to address more fully the issue of reproductive risks. The potential adverse effects in the very young following exposure to CS was addressed also by Park and Giammona,[407] who have described the effects of CS in a 4-month-old infant after prolonged exposure. The infant manifested severe respiratory distress and symptoms included copious nasal and oral secretions, sneezing and coughing and obstruction of the upper airways. The patient was released from hospital yet within 24 h was rehospitalized with a diagnosis of pneumonitis. The patient was treated and released following a 28-day hospitalization. Additional documentation pertaining to the health effects of CS following its application in riot control and law enforcement situations is that of Anderson et al.[408] 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. During this civil disturbance, large quantities of CS were utilized in a confined space 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 following exposure with possible CS-related symptoms were reviewed. Findings indicated that the most common complaint was coughing. Although

the majority of patients had recovered completely within 2 weeks of exposure, one asthmatic child had sore throat and shortness of breath. This condition persisted for 38 days following exposure to CS. Additionally, a 3-month-old infant with confirmed hematemesis was admitted to the hospital for observation. Because there was a 6–8-h delay from exposure to presentation at the clinic, the immediate and transient effects of lacrimation and rhinorrhea were not reported. A high incidence of skin burns was noted among the CS-exposed individuals, 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 under conditions of high humidity was a cause for concern. Anderson et al.[408] confirmed the findings of the Himsworth Committee,[404,406] at least with respect to the transient nature of riot control agent-induced effects involving the eye and upper respiratory tract.

In spite of its extensive use, there have been no verified causes of death in humans following CS application.[6,29,61] There have been several alleged reports of death following CS exposure but these were non-verifiable and/or incorrect. Hu[10] reported that a middle-aged adult suffered heart failure and hepatic damage on exposure to CS and had eventually succumbed. A review of the original report of the incidence by Krapf and Thalmann[409] indicated that the subject did indeed suffer heart failure and hepatic insult. This individual was hospitalized, treated and discharged 3 months after the exposure in a condition capable of work. Another report on the subject of CS-related fatality was a GAO document that focused on allegations that the Israeli Defense Forces had mis-used US-manufactured CS.[410] The alleged misuse was reported to have caused numerous deaths, principally among the sick and elderly. The majority of casualities were purported to be <1 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.[411] In addition, the US 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. Furthermore, Israel was utilizing two types of tear gas, but generally employed CN. Hence, it is believed that the allegations of death following the use of CS in the West Bank and Gaza were unsubstantiated. According to Ballantyne, there are no authorized reports of death from CS smokes.[29] Published estimates of the human acute lethal inhalation dosage of CS vary between 25 000 and 150 000 mg·min m^{-3}. A widely quoted estimate of the human LCt_{50} for CS is 61 000 mg·min m^{-3}, which is from US sources. For humans, lethal dosage estimates can be derived only by extrapolation from animal data because humans can withstand only minute dosages of riot control agent. Furthermore, in light of the variance in the lethal dose response noted in various animal species, conservative values should be adopted. In addition, it must be recognized that estimates of lethal amounts on the basis of deaths occurring in law enforcement operations can be quite imprecise. The Himsworth Report[404] concluded that the physical properties of CS smoke and the unpleasant nature of the symptoms produced exposures that were self-limiting and short. 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, because a condition of adaptation occurs and the irritant effects are diminished. The irritant ICt_{50} for CS that is considered intolerable for 1 min is 0.1–10 mg m^{-3}. However, the exact concentration depends on the individual's degree of motivation.[61]

Dibenz[b,f]1 : 4-oxazepine (CR). A number of investigators[19,52,57,72–74,412,413] have reported on the effects of CR on human subjects following aerosol exposures, 'drenches' with dilute solutions and local application. The estimated human LCt_{50} of CR is >100 000 mg·min m^{-3}. Human studies have been conducted to determine the effects of CR after aerosol or cutaneous exposures, and the findings are 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 included lacrimation, irritation and conjunctivitis; and respiratory effects included upper respiratory tract irritation and associated choking and dyspnea. Ballantyne et al.[57] described the effects of dilute CR solutions following 'splash contamination' on the face. In addition to the classical effects on the eye, CR facial 'drenches' also produced an immediate increase in blood pressure concomitant with decreases in heart rate. Subsequent studies to ascertain the effects of CR after whole-body 'drenches' also were conducted by Ballantyne and co-workers.[74] Immediate increases in blood pressure were noted, as in the previous study; however, Ballantyne et al.[74] concluded that the cardiovascular effects described in both studies were not due to CR. 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[246,247] suggested that the cardiovascular effects described by Ballantyne and co-workers[57] were the result of CR-induced effects on the heart via the sympathetic nervous system. Ashton et al.[413] also had studied the effects of CR aerosol on the respiratory physiology of humans. Test subjects were exposed to CR aerosol of particle size 1–2 μm at a mean concentration of 0.25 mg m^{-3} for 1 h. Expiratory flow rate was decreased ∼20 min after onset of exposure. The authors postulated that CR stimulated the pulmonary irritant receptors to produce bronchoconstriction and increased the pulmonary blood volume by augmenting sympathetic tone.

Chloroacetophenone (CN). Initially, the LCt_{50} estimate of CN for humans was set at 7000 mg·min m^{-3} and subsequently was revised and established as 14 000 mg·min m^{-3}. In human volunteer studies, the immediate effect on exposure to CN was a burning sensation or stinging in the eyes, nose, throat and exposed skin. Immediate symptoms were followed by lacrimation, salivation, rhinorrhea and dyspnea. Lacrimation persisted for ∼20 min post-exposure whereas conjunctivitis and blepharospasm persisted for up to 24 h. High levels of CN can produce chemical injury to the eye, which is characterized as corneal and conjunctival edema, chemosis and loss of corneal epithelium.[59] Physical injuries also may occur following dispersion via grenade-type tear gas devices.[34,59] Punte and co-workers[414] studied the effects of CN on human

subjects. Individuals were exposed to CN aerosol at a Ct of <350 mg·min m^{-3}, which is considered the maximum safe inhaled dosage for humans. Common symptoms included 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 ~10 min from cessation of exposure.

The incapacitating dosage (ICt_{50}) of CN has ranged from 20 to 50 mg·min m^{-3}. The ICt_{50} of CN is comparable to DM, an early riot control agent that CN replaced. However, the ICt_{50} value for CN is considerably greater than the ICt_{50} of CS, which replaced CN in turn. The estimate for the human LCt_{50} of CN dispersed from grenades is 7000 mg·min m^{-3}—other reported estimates are in the range 8500–25 000 mg·min m^{-3}.[61] According to Punte et al.[60] the maximum safe inhaled dose of CN for man is estimated at 500 mg·min m^{-3}. As reported by Thorburn,[415] pulmonary lesions may occur at the inhalation dosages and the effects of CN exposure in confined spaces can be severe. Exposed individuals manifested lacrimation, conjunctivitis, conjunctival edema, upper respiratory tract irritation, cough, dyspnea and skin burns. Death from high concentrations of CN may occur and the post-mortem examination may reveal edema and congestion of the lungs, alveolar hemorrhage, necrosis of the mucosal lining of the lungs and bronchopneumonia.[416,417] Lethal exposures to CN have been reported.[415–417]

Adamsite (DM). The human toxicology of DM has been reviewed by Owens et al.,[251] McNamara et al.[61] and Ballantyne.[29] The earliest human study on the effects of DM was that of Lawson and Temple,[418] which described the DM-induced effects following inhalation exposure. The human toxicology of DM was revisited in studies by Gongwer et al.[419] and Punte et al.,[414] who 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 mg·min m^{-3}, which was considered the maximum 'safe' inhaled dose for man, and 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 upon termination of exposure. Based on their findings, Punte et al.[414] estimated that the ECt_{50} for irritation (3-min exposure) was 19 mg·min m^{-3}. The dosage (Ct) required to elicit vomiting and nausea, however, could not be established. Additional human toxicological data were reviewed by McNamara et al.[61] McNamara cited a dosage of 49 mg·min m^{-3} as necessary to cause vomiting and nausea, based on human studies where individuals were exposed to DM at $Ct = 7$–236 mg·min m^{-3}. High confidence in the above estimate, however, is lacking because the estimate was based on a highly variable dataset. Ballantyne[29] had estimated a dosage of 370 mg·min m^{-3} to elicit nausea and vomiting. Inhalation of high concentrations of DM has resulted in severe pulmonary damage and death.[250]

GENERAL 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 CN and DM have been replaced with 'safer' compounds such as CS and OC. As much is known of the toxicity of riot control agents such as CS as for many regulated chemicals such as pesticides. Substantial evidence suggests that riot control agents are safe when used as intended. 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 is 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 lethalities 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 because 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 but 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 research to define and delineate the biological and toxicological actions of riot control agents and to illuminate the full health consequences of these compounds.

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