APPENDIX D:
CS

ADVERSE HEALTH EFFECTS FROM CS

General Reviews / Comments

Punte et al (1963), from the US Army Chemical Research and Development Laboratory, reviewed CS.[1] Acute and subacute studies by Punte et al (1962) have shown that CS has low toxicity administered by the intravenous, subcutaneous or inhalation routes. Autopsies performed on animals killed after the inhalation of CS revealed minimal pathology. The salient finding was an increase in the number of respiratory tract goblet cells following exposure to high concentrations of CS (20,000 to 30,000 mg per minute per cubic metre).

An editorial in the BMJ (1971) discussed the Himsworth Report (1971) of CS.[2] It considered that the Report found that CS was remarkably non-toxic. Although, the Report did mention that CS can cause blistering of the skin and acute exacerbations of chronic bronchitis. The Report considered that a person confined to a small, unventilated room with no means of escape might be exposed to dangerous levels of CS if a standard 12.5 g canister disseminated its full dose. It also noted that if all inhaled CS were retained and all converted to cyanide, the total amount derived from exposure for one minute to 10 mg per cubic metre of CS - a level that is normally intolerable - was less than that derived from two puffs of a cigarette. Jones (1971) commented on this matter, noting that CS appeared to have a different mechanism of action depending on the route of exposure.[3] Exposure via injection appeared to act via cyanide while another mechanism of action was relevant in inhalational exposure.

An editorial in the Lancet (1971) also discussed the Himsworth Report (1971) of CS.[4] It noted that CS might cause an acute exacerbation of chronic bronchitis or an attack in a person that suffers from asthma. Abortion, stillbirth, and congenital abnormality records for Derry did not suggest that CS interfered with pregnancy. Chromosome changes in human white blood cells were not seen. The editorial noted that there was no convincing evidence that CS contributed to death in humans when used for riot control purposes. But it did mention the testimony of a Canadian medical officer who had worked in Vietnam; CS driven into shelters caused delayed death from lung damage in about half of the 20-30 patients hospitalised.

Jones (1972) reviewed CS and its chemical relatives.[5] CS is 2-chlorobenzylidene malononitrile and is a member of the group of compounds known as benzylidene malononitriles (BMNs). BMNs were produced from the condensation of benzaldehyde and its derivatives with malononitrile. BMNs are solid crystalline materials and have been used in various applications; chemotherapeutic treatment of cancer, pesticides, fungicides, and insecticides. BMNs form adducts with many substances although of varying stability. CS was prepared by Corson and Stoughton, hence the name. The airborne form of CS is almost entirely an aerosol, hence the term

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[1] Punte C, Owens E, Gutentag P (1963). Exposures to ortho-chlorobenzylidene malononitrile. Controlled human exposures. Archives of Environmental Health 6: 72-80. ID 26680
[2] Anonymous (1971). Verdict on CS. BMJ 3: 722. ID 27404.
[3] Jones G (1971). Re: Verdict on CS. BMJ 4: 170. ID 27403.
[4] Anonymous (1971). Toxicity of CS. Lancet Sept 25: 698. ID 27517.
[5] Jones G (1972). CS and its chemical relatives. Reprinted from Nature 235: 257-261.

CS "gas" was considered misleading. The author discussed the literature on human exposure to CS. Reference was made to unpublished data describing allergic contact dermatitis in workers in chemical plants exposed to CS (Weigand 1969, Military Medicine). The mechanism of action was thought to involve an altered antigenic profile of serum proteins, resulting from the formation of -SH adducts with CS. CS was said to produce erythema of the eye, severe conjunctivitis, intense burning of the skin, and with heavy cutaneous exposure erythema and vesiculation of the skin that resembled second-degree burns (Punte et al 1963, Archs Environ Health). Reports of coughing, burning of the throat and chest constriction were also noted (Punte et al 1963, ibid; Finn et al 1964, Brit. Patent). Another study reported racial differences from exposure to CS aerosol at high humidity and 37 degrees (Hellreich et al 1967, Technical Report). In black subjects, erythema was the most serious sign while in white subjects, widespread blistering occurred some days later, and scarring was observed six weeks after exposure. There was a report of subjects having difficulty in keeping their eyes open after initial exposure to CS but visual acuity was not noticeably affected (Rengstorff 1969, Military Medicine).

Jones (1972) then discussed the literature on animal exposure to BMNs and CS.[6] Early studies reported that various BMNs had growth-retarding effects on transplanted tumours in mice and CS was observed to cause irritation (Gal and Greenberg 1951 Amer Chem Soc; Gal et al 1952 Cancer Res). A study on rats, mice, guinea-pigs, rabbits and pigeons that exposed these animals to lethal doses of CS reported severe erythema of the eyes and conjunctivitis, although no permanent eye damage was observed and all animals were killed within five weeks of exposure (Punte et al 1962, Toxic Appl Pharmac). Other observations from this study included an increase in goblet cells of the conjunctiva and respiratory tract, necrosis at sites of impact from CS particles in the gastro-intestinal and respiratory tracts, pulmonary oedema and adrenal gland haemorrhage occasionally, especially at high inhalation doses. Another study on anaesthetised dogs that used lethal doses of CS aerosols, observed initial increases in blood pressure and respiratory rate and the dogs died in respiratory distress two to three days later. Pulmonary oedema, haemorrhage and atelectasis were found in the lungs of exposed dogs. A study on monkeys observed the effect of CS aerosol at four doses (2.7, 8.5, 28.5, 80 mg min/L) (Striker et al 1970; Chem Abstr). Pulmonary congestion, bronchorrhoea, emphysema, and atelectasis occurred at the two lower doses. These cleared after three days but recurred one and four weeks after exposure. At the third highest dose, bronchopneumonia was observed one week after exposure. At the highest dose, lesions were visible on x-ray. Emphysema, atelectasis and bronchiolitis were observed in most survivors, killed up to 30 days after exposure. A study on cats and dogs exposed to small doses of CS (50 to 200 ug/kg) via intravenous injection, found that CS was a non-specific irritant and affected the blood pressure (Biscoe and Shephard 1962, Archs Intern Pharmacodyn Ther).

An editorial in the BMJ (1973) discussed the potential for carcinogenicity of CS.[7] It noted the results of Barry and colleagues (1972) that CS suppressed the non-specific

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[6] Jones G (1972). CS and its chemical relatives. Reprinted from Nature 235: 257-261.
[7] Anonymous (1973). Tests on CS for carcinogenicity. BMJ 1: 129. ID 27402

esterase activity in the sebaceous glands of mouse skin.[8] [9] The editorial called for long-term carcinogenicity studies.

Brimblecombe et al (1972) [from the Chemical Defence Establishment, Porton Down, UK] studied the pharmacological effects of CS on isolated organs, anaesthetised animals (cats, dogs, rabbits) and cat encephale isole preparations.[10] They found that in the cat encephale isole preparation, intravenous CS at 1 mg/kg produced brief electrocortical alerting but no abnormal activity in EEG. Doses in excess of 10 mg/kg produced cortical depression. Intravascular injection of CS into the chloralose anaesthetised cat typically resulted in a pressor response accompanied by a brief period of apnoea. The threshold dose for the pressor response varied with the route of intravenous administration; but generally was between 2.5 and 12.5 ug/kg. The threshold dose for apnoea was slightly higher. Variations in this pattern of response were seen in other animals (dogs and rabbits) and with other anaesthetics. When CS was administered by stomach tube to chloralose anaesthetised cats, no measurable effects were demonstrated at doses up to 100 mg/kg. No changes in blood pressure or respiration were detected in anaesthetised cats given pure CS aerosol for one hour in concentrations of between 345 mg per cubic metre and 1.39 g per cubic metre via tracheal cannula or through the upper respiratory tract. Pure CS solution given by slow intravenous infusion at a similar dose and over a similar period produced significant effects on blood pressure and respiration. Pyrotechnically generated (grenade) CS produced variable effects when given by inhalation in concentrations of between 460 and 1,040 mg per cubic metre for one hour. Respiratory depression regularly occurred when grenade CS inhalation was via the upper respiratory tract. Respiratory stimulation was observed when grenade CS inhalation was via tracheal cannula. Ten of twelve cats exposed to high concentrations of grenade CS inhalation via the upper respiratory tract showed an immediate transient increase in blood pressure. This was not seen in cats exposed to lower concentrations. The authors noted that extrapolation to humans of results obtained using anaesthetised cats may not be completely appropriate. They noted exposure for more than 30 minutes to CS in a 20 cubic metre room with low natural ventilation, generated from a L2A2 cartridge that contained 12.5g of CS, would not result in a total dose that exceeded 6,000 mg per minute per cubic metre. In their experiments, high concentration of grenade CS ranged from 26,590 to 62,630 mg per minute per cubic metre while low concentration varied from 3,650 to 4,310 mg per minute per cubic metre. Animals exposed to lower concentrations showed certain effects (ie respiratory depression) but these did not progress after exposure was terminated and when animals were observed for more than 30 minutes after the exposure there was a tendency for recovery in all measured parameters.

Sanford (1976) reviewed riot control agents.[11] The author noted that there were two general types of tear gas devices; pressurised type and explosive cartridge type. Grenades mix CS with a pyrotechnic composition, and when this was detonated, an

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[8] Barry D, Chasseaud L, Hunter B, et al (1972). The suppression of non-specific esterase activity in mouse skin sebaceous gland by CS gas. Nature 240: 560-1. ID 27510
[9] Chasseaud L, Hunter B, Robinson W, et al (1975). Suppression of sebaceous gland non-specific esterase activity by electrophilic alpha beta-unsaturated compounds. Experientia 31: 1196-7. ID 27509
[10] Brimblecombe R, Green D, Muir A (1972). Pharmacology of o-chlorobenzylidene malononitrile (CS). Br J Pharmac 44: 561-576. ID 27565
[11] Sanford J (1976). Medical aspects of riot control (harassing) agents. Ann Rev Med 27: 421-429. ID 26770.

aerosol was generated. A grenade would generate a cloud of 20 to 30 feet in diameter on a calm day and this could linger for 10 to 15 minutes.

Ballantyne (1977) reviewed the use of chemicals, including CS, in civil disturbances. CS was used in pyrotechnic compositions [such as potassium chlorate, lactose, and kaolin] in grenades and cartridges that generated smokes.[12] CS has also been used as powder formulations, CS1 and CS2, in explosive burst or fogging machines. CS1 was a micronised powder formulation containing 5% hydrophobic silica aerogel, which persists for about two weeks in normal weather conditions. CS2 was a siliconised microencapsulated form of CS1, composed of 95% micro-pulverized CS with silica treated with hexamethyldisilazane. Two phases of skin erythema have been described in humans after contamination with CS solutions. Immediate erythema appeared within a few minutes and persisted for less than an hour. However, delayed erythema occurred about two hours later and persisted for 24 to 72 hours (Weigand et al 1969). Several factors can influence the severity of the skin reaction to CS such as race (Caucasian > Negro), heat and humidity (worse with high temperature and humidity). It was reported that CS does not affect the healing of cutaneous wounds or burns (Ballantyne and Johnston 1974). Abortion, stillbirth and congenital abnormality records from Derry showed no association between CS exposure and interference with human pregnancy (Lancet 1971). In healthy male volunteers, no change in pulmonary gas transfer or alveolar volume was observed after exposure to CS aerosols under controlled conditions, but a reduction in exercise ventilation volume was noted (Cotes et al 1972). No change in lymphocyte chromosome morphology was also observed after exposure to CS aerosols (Holland and Seabright 1971). Prolonged high exposure to CS in confined spaces with no ventilation could result in respiratory tract inflammatory changes and associated secondary infection (Park and Giammona 1972). There was also felt to be a risk of exacerbation in those with chronic bronchitis or asthma. Acute effects resulted from a peripheral sensory irritant effect, an interaction with sensory receptors in the skin and mucosae. The mechanism of toxicity was said to vary with the route of administration: oral route - haemorrhage and fluid loss; parenteral - cyanogenic property of malononitrile and SN_2 alkylation effects; inhalation - lung damage. While CS was absorbed from the respiratory tract (Leadbeater 1973) and urinary thiocyanate excretion was elevated in animals exposed to CS, the lethal toxicity of inhaled CS was considered to be by lung damage. The amount of cyanide produced by an exposure dose, which an individual could tolerate, was thought to be negligible.

Beswick (1983) [from the Chemical Defence Establishment, Porton Down, UK] discussed chemical agents used in riot control and warfare.[13] Riot control agents, including CS, were said to cause pain by direct action on nerve endings. CS2 reported to have been used in Vietnam (a mixture of CS powder with an agent such as Neocil). The lethal dose of CS was 60,000 mg min per cubic metre, estimated from studies on small laboratory species. Primary contact dermatitis amongst laboratory workers exposed to CS was reported as rare. The main risk from CS was said to come from secondary bronchopneumonia a day or so after prolonged exposure to CS in an enclosed space.

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[12] Ballantyne B (1977). Riot control agents. Biomedical and health aspects of the use of chemicals in civil disturbances. Medical Annual, Bristol UK: Wright and Sons, p 7-41. ID 26881.
[13] Beswick F (1983). Chemical agents used in riot control and warfare. Human Toxicol 2: 247-256. ID 26804.

Danto (1987) discussed the use of tear gas by police.[14] The author noted that the tear-gases, CS and CN, may cause fires to be ignited and this in turn carries the potential for death from smoke inhalation. The author mentioned a case of the US police firing some 40 shells of tear-gas [type not specified] into the home of an agitated man over a two-hour period. This ignited a house fire and the man died from smoke and tear gas inhalation.

Hu et al (1989) reviewed tear gas, especially CS.[15] [16] The authors visited Seoul, South Korea, in July 1987. Political demonstrations that led to the use of tear gas had occurred in the preceding month. A mass spectrometry analysis of a sample showed that it was pure CS. The authors interviewed and examined over a hundred people, including individuals exposed to tear-gas, hospital staff, and bystanders. Individuals close to exploding tear gas grenades and canisters commonly sustained penetrating trauma from plastic fragments. There were reports of blistering skin burns from direct contact with the tear gas powder. Shopkeepers and their families in communities near where the demonstrations took place complained of cough and shortness of breath that persisted for several weeks. Hospital physicians reported that patients with asthma and chronic obstructive lung disease exposed to tear gas through open hospital windows, experienced clinical deterioration in lung function. Oral toxicology studies in animals reported severe gastroenteritis with perforation [Ballantyne and Swanston 1978, Gaskins et al 1972]. CS was reported as questionably mutagenic in the Ames assay on Salmonella [Zeiger et al 1987]. CS was reported to suppress non-specific esterase activity in mouse skin sebaceous gland [Barry et al 1972, Chasseaud et al 1975]. An increase in pulmonary tumours in A/J strain mice and Sprague-Dawley-Wistar rats exposed to CS in four-week inhalation experiments [at 0, 50, 500 mg per cubic metre per minute] was observed [McNamara et al 1973]. The increase was reported as not strictly dose related and of borderline statistical significance. The report concluded that CS was not significantly tumorigenic in these animals. Chemical pneumonitis, pulmonary oedema, heart failure, hepatocellular damage and death have been reported in adult humans after high-level exposure to CS [Himsworth Report 1971; Report on the Status of Palestinian Children: Uprising in the Occupied Territories (9 Dec 1987- 9 Dec 1988), Save the Children; Krapf and Thalmann 1981 - German case report].

Wheeler and Murray (1995) from their experience at the National Poisons Information Service (London), stated that in most circumstances only short term health effects were associated with exposure to CS, but long-term health effects can occur.[17] These authors also mentioned other case reports. Lau et al (1994), at the Fifth World Congress of the World Federation of Associations of Clinical Toxicology Centres and Poison Control Centres, reported on 184 Vietnamese people at a detention camp. They complained of cough, burns, shortness of breath, chest pain, sore throat, and fever and all but one had recovered within two weeks. Coughing,

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[14] Danto B (1987). Medical problems and criteria regarding the use of tear gas by police. American Journal of Forensic Medicine and Pathology 8: 317-322. ID 26908.

[15] Hu H, Fine J, Epstein P, et al (1989). Tear gas - harassing agent or toxic chemical weapon? JAMA 262: 660-663. ID 26790

[16] Hu H (1992). Toxicodynamics of riot-control agents (lacrimators). In: Chemical Warfare Agents ID 28229

[17] Wheeler H, Murray V (1995). Poisons centre will monitor cases (Letter). BMJ 311: 30th September.

wheezing, and dyspnoea persisted for two years after short-term exposure in a previously well 21-year old woman (Hu et al 1992). Two cases of allergic dermatitis confirmed by patch testing were reported by Ro and Lee (1991) after exposure to tear gas.

Jones (1996) discussed decontamination after exposure to CS sprays.[18] In this article he mentioned an early study of young volunteer soldiers exposed to CS aerosols that observed that white skin developed erythema and bullae more readily than black skin.

Sidell (1997) discussed riot control agents, including CS.[19] He noted that the concentration of CS that incapacitated 50% of the exposed population was 3-5 mg per minute per cubic metre. The concentration of CS that was lethal to 50% of the exposed population was quoted as 60,000 mg per minute per cubic metre. Ongoing sequelae discussed included irritant and allergic contact dermatitis. The author described the case report of the infant exposed to high concentration of CS aerosol in an enclosed space who developed delayed pneumonitis (Park and Giammona 1972). He also stated that people with chronic bronchitis had been exposed to CS without untoward effects, but any underlying lung disease eg asthma might be exacerbated by exposure to CS.

Jones (1997) discussed whether CS sprays were safe.[20] He mentioned that the Himsworth Committee (1969/71) had approved the use of CS aerosols, but not sprays, for use in civil disturbances in England and Wales. In 1996, CS sprays were trialed in certain areas of England and Wales. The author pointed out that there was a substantial difference between the tiny quantities of CS contained in an aerosol and the much larger amounts contained in a 5% w/v spray and to extrapolate from aerosols to sprays was not justified. The author also considered that cool fresh air in a decontaminated area would remove CS particles from an exposed person if an aerosol was used but this would not be effective for a spray. The author noted that the immediate effects of CS was intense pain in the eyes and sensitive areas of the face, followed later by blistering, dermatitis and allergic sensitisation, depending on the extent of exposure. A report of the police scientist who had cleared CS spray for use and who had developed facial blistering was noted. A police inspector suffered 40% burns to one eye and 50% burns to the other eye during training. Possible effects on breathing including the risk of respiratory arrest were also noted.

An editorial in the Lancet (1998) discussed the safety of CS.[21] It mentioned that in mid-1996, some British police forces began to use CS spray, in the form of CS crystalline solid (o-chlorobenzylidene malononitrile) dissolved as 5% w/v in methyl isobutyl ketone (MIBK), with nitrogen as a propellant. It was noted that in the US, CS was used at one fifth of this concentration. Acute effects listed included pain in the eyes, lacrimation, blepharospasm, a burning sensation in the nose and throat, nasal secretion, salivation, constriction of the chest, sneezing, coughing, retching and a burning feeling on the exposed skin. Acute effects were said to lessen within 15

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[18] Jones G (1996). CS sprays: antidote and decontaminant. Lancet 347: 968.
[19] Sidell F (1997). Chapter 12 Riot Control Agents. In: Textbook of Military Medicine Part 1: Medical Aspects of Chemical and Biological Warfare. Zajtchuk (Ed). Office of the Army Surgeon General, Washington, DC. ID 27592
[20] Jones G (1997). Are CS sprays safe? (Commentary). Lancet August 30: 605.
[21] Editorial (1998). Safety of chemical batons. Lancet 352: 159. ID 23891.

minutes. However, the editorial mentioned that there were reports of more chronic effects on the skin [extensive blistering and burning] and eyes. In British police officers, one suffered 50% burns to the eyes after having trained with CS spray, others developed "dry eye" after a demonstration of CS sprays, and skin reactions have been observed on hands. From France, there have been reports of severe skin reactions [erythematous dermatitis on exposed areas with vesicles, blisters, and crusts] and keratitis. It was questioned whether the toxic effects were due to the CS component of the spray or the solvent, MIBK. It was considered that the safety profile of this formulation of CS was under investigated.

The material and safety data sheet for tear gas produced by QUALCO products was obtained (last review 1998).[22] Ingredients were stated to consist of o-chlorobenzylidene malononitrile (% weight < 1) and mineral oil (% weight > 90). Routes of entry were stated to be inhalation and by skin. Symptoms and signs of overexposure were stated to be for inhalation: irritation, burning of nose/throat, coughing, nasal discharge, sneezing, headache, and dizziness. For skin: stinging or burning of contact areas and tightness of chest. Ingestion: nausea, vomiting in high concentrations. Eye: burning sensation, heavy flow of tears, involuntary closing of eyes. The manufacturer did not specify that any medical conditions were aggravated by exposure. A disclaimer appeared at the end of the safety data sheet, stating that this information was formulated for use by elements of the US Department of Defence.

The British Department of Health (1999) produced a report on CS, in view of concerns about possible health effects arising from the introduction of the use of CS spray by police in 1996.[23] Their conclusions follow. One limitation of the report is a lack of discussion about the possibility of any long-term respiratory sequelae in humans, (apart from references to aggravation of asthma) and a limited review of human data on ocular effects.

> *47. The Committee noted that there are considerable data available to assess the toxicity of CS itself, and to a lesser extent, the solvent MIBK itself. CS is a potent sensory irritant, particularly to the skin and the eyes. It is rapidly hydrolysed and therefore tissue exposure to CS itself is transient. Experience in use indicates that it is a skin irritant and there are some reports of skin sensitisation occurring. There are no concerns relating to the mutagenicity, carcinogenicity or teratogenicity of CS itself. The toxicity of the solvent MIBK is characterised by transient local irritant effects and central nervous system (CNS) effects (particularly headache, nausea) resulting from occupational exposures of about 100 ppm and above. Negative results were obtained in mutagenicity tests and there was no evidence of teratogenicity in developmental toxicity studies. There is no information from carcinogenicity or multigeneration reproductive toxicity assays.*

> *48. There are very few data on the formulated material. A 7% (w/v) solution of CS in MIBK produced severe irritant effects in rabbit eyes followed by recovery in 8 days. This is consistent with the absence of evidence of serious permanent eye*

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[22] Medical Safety Data Sheet. Cornell University. http://msds.pdc.cornell.edu/msds/siri/files/chl/chlfz.html. Accessed 12/12/2002. ID26479

[23] Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products, and the Environment (1999). Statement on 2-chlorobenzylidene malononitrile (CS) and CS spray. London: Department of Health, 1999. www.doh.gov.uk/pub/docs/doh/csgas.pdf

damage in humans. Experience in use indicates that it has skin irritant properties, and can cause dermatitis.

46. Literature searches did not reveal reports of serious eye damage caused by CS spray. Furthermore such cases were not identified as a consequence of exposure to CS spray in the data provided by NPIS London Centre.

49. The Committee's conclusions regarding the health effects of CS spray were based on consideration of the toxicity data on CS and MIBK. As noted above there was very little information on the formulated product. The Committee's advice applies to all individuals exposed to CS spray during its use as a chemical incapacitant.

50. The Committee considered that the available data did not, in general, raise concerns regarding the health effects of CS spray itself. Local irritant effects are short term and there exists the possibility of skin sensitisation occurring in some individuals. It must be noted that no comprehensive investigation of the effects of CS spray in humans was available, nor has there been any systematic follow-up of individuals who have been sprayed with CS spray.
The Committee has concerns regarding exposure to CS spray in susceptible groups. These are:

- *Individuals with bronchial asthma or chronic obstructive airways disease whose condition could be aggravated by the irritant effects of CS spray on the respiratory tract.*
- *Individuals suffering from hypertension or other cardiovascular disease because of the transient effects of CS spray in increasing blood pressure.*
- *It was not possible, on the basis of the available data, to comment on whether individuals being treated with neuroleptic drugs are more likely to be sensitive to the effects of CS spray.*

The British Department of Health Report (1999) noted that the toxic effects of CS spray depended in part on how far any CS droplets produced can penetrate into the respiratory tract.[24] The latter in turn depended on the mass and size of the droplets of CS solution in MIBK produced during spraying. A study was commissioned to investigate this matter and findings are reproduced as follows. Comments made in paragraph 11 concerning the unlikelihood of static air conditions may not be relevant to the operational environment in which SASR CT training occurred.

9. The Committee was of the view that, although the CS canisters release, for the most part, a coarse spray, there is a proportion of droplets with diameters of less than 100 μm which, in the event of full discharge of the can, could transport a maximum of 20 mg of the spray solution into the upper respiratory tract the smallest droplets of which (diameter 28 to 50 μm), could reach the large- and medium-sized airways of the lung. This proportion will be increased if the spray is scattered from any nearby surface. Since these are the airways that are affected in bronchial asthma, it is possible that an asthmatic attack could occur in susceptible

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[24] Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products, and the Environment (1999). Statement on 2-chlorobenzylidene malononitrile (CS) and CS spray. London: Department of Health, 1999. www.doh.gov.uk/pub/docs/doh/csgas.pdf

individuals. It was also recognised that the increased rate and depth of respiration occurring in an individual under stress might, in addition, result in a greater dose of the CS spray being inhaled.

10. In a separate study with CS canisters the vapour concentration of the solvent MIBK was measured at 6 positions placed either as close as could be achieved or up to 0.5 m from a target. The target was sprayed from a distance of 2.0 m for periods of 1 or 3 seconds or until the canister was empty. The resultant MIBK vapour concentration at each position was then measured at one second intervals for a period of 15 minutes. In these trials the Short Term Exposure Limit (STEL)* for MIBK of 100 ppm time-averaged over a 15 minute reference period6 was exceeded on four out of eighteen occasions. However, static air conditions were used in these trials in order to achieve a greater reproducibility,4 such conditions would reduce dispersion and increase average measured concentrations.

11. Because of the nature of this trial, and the differences in circumstances from operational use where static air conditions would be unlikely, the Committee felt that these results probably did not represent a cause for concern, provided that the spray is used in accordance with the operational guidelines.

* Short Term Exposure Limit (STEL): An occupational exposure limit defining a level of exposure over a 15 minute reference period which should never be exceeded.6 Such values are typically set to protect workers against effects that occur rapidly after exposure eg irritation of the eyes, nose and throat.

The nature of CS spray and its components

4. The CS spray used by police forces in the UK consists of a 5% (w/v) solution of CS in MIBK, comprising 1.5 grams (g) of CS dissolved in a total volume of 30 millilitres (ml), contained in a canister with nitrogen as a propellant.

Other relevant sections of this British Department of Health Report (1999) include a literature review on the toxicity of CS, MIBK and the combined formulation and are reproduced as follows[25]:

Toxicity of CS

12. Most of the data on the toxicity of CS derive from studies which have used either CS aerosols or pyrotechnically-generated 'smokes'. In both cases respirable particles were produced. Data have been obtained on the size of droplets resulting from the use of CS dissolved in an organic solvent and delivered in the form of a spray; these are discussed in paragraphs 7 to 9 above.

Metabolism

13. Studies of the metabolism of CS have been conducted on the compound itself and not in the form in which it would be used as an incapacitating agent by police

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[25] Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products, and the Environment (1999). Statement on 2-chlorobenzylidene malononitrile (CS) and CS spray. London: Department of Health, 1999. www.doh.gov.uk/pub/docs/doh/csgas.pdf

officers. It is readily hydrolysed in aqueous mixtures[7,8] and reacts readily with plasma proteins and glutathione in vitro and in vivo.[9,10] It undergoes rapid metabolism and chemical breakdown in vitro and in vivo, initially to 2-chlorobenzaldehyde and malononitrile, each of these then undergo further rapid reactions. The half lives ($t_{½}$) of CS and the metabolites, 2-chlorobenzaldehyde and 2-chlorobenzylmalononitrile in one in vivo experiment involving the administration of compounds by intra-arterial injection into cats were 5.4, 4.5 and 9.5 seconds respectively.[11] After oral administration CS is metabolised and eliminated largely (circa 70%) via the urine as 2-chlorohippuric acid and 2-chlorobenzoic acid.[12] Other metabolites have been identified but there is no evidence of dechlorination. It was noted however that the available data were not as comprehensive as would have been obtained if modern techniques had been used. In addition, no data were available on the kinetics of CS administered as a solution in MIBK.

Experimental studies in animals

14. The acute toxicity of CS following exposure via inhalation is characterised by sensory irritancy followed by prompt recovery. Acute studies in rodents and guinea pigs using pyrotechnically-generated CS smokes indicated that short term exposure (10 to 20 minutes) to concentrations of CS of around 4 grams/metre[3] (g/m^{3}), or longer exposure (several hours) to levels of around 30 to 40 mg/m^{3}, resulted in deaths. Death was due to severe lung damage (comprising haemorrhages and oedema).[13] Animals that survived showed no pathological abnormalities when examined 14 days later.

15. Studies to investigate skin irritancy in rats, rabbits and guinea pigs indicated that a 12.5% (w/v) solution of CS in corn oil or acetone applied for 6 hours without occlusion produced mild skin irritation.[7] No conclusions can be drawn with regard to its potential to induce skin sensitisation from the two animal studies available due to limitations in the methodology used.[14,15] There are, however, some data in humans to indicate that CS can provoke skin sensitisation (see paragraph 30).

16. The eye irritancy of CS has been shown to be dependent upon the solvent used. A 5% (w/v) solution in PEG-300 (polyethylene glycol) produced severe irritant effects in the rabbit (mild or moderate keratitis lasting for 2 weeks or more after a single application) whereas a 10% (w/v) solution in trichloroethane produced some conjunctivitis but no corneal damage and no effects were seen after 7 days.[16,17] Results of eye irritancy studies in rabbits using a 7% (w/v) solution in MIBK are given in paragraph 44; signs of severe irritation were seen initially with recovery after 8 days.

17. Repeated dose inhalation studies involving exposure for 1 hour a day for 120 days, indicated a NOAEL[*] of about 30 mg CS/m[3] in a range of species (mice, rats, guinea-pigs).[18] At around 200 mg/m^{3} in mice and guinea pigs, deaths of 23% and 48% respectively of the exposed animals occurred in the first month of the experiment.

[*] No Observable Adverse Effect Level

Mutagenicity

18. The mutagenicity data on CS were considered by the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM). Their conclusions are given in the following paragraphs.

In vitro studies

19. The mutagenicity of CS has been extensively studied in vitro. Negative results were obtained in Salmonella assays, but there were reservations regarding the suitability of the standard protocols used in these tests with respect to CS in view of its very short half life.[19-23] Positive results were noted in assays in V79 cells for gene mutation and also in the mouse lymphoma assay.[20,24,25] Positive results were documented also in metaphase analysis for clastogenicity in V79 and CHO cells.[20,26] In addition, CS has been shown to induce SCEs (Sister Chromatid Exchanges) in CHO cells.[20] These data indicate that CS has clastogenic potential.

20. There is evidence from in vitro studies to indicate that CS has aneugenic effects. It has been shown to interfere with the spindle machinery and cell division in mammalian cells resulting in C-mitosis and metaphase block.[27-32] CS has also been shown to induce micronuclei in mammalian cells in vitro.[25] These data suggest that CS has aneugenic potential.

21. The clastogenic effects seen appear to be due to CS itself, or an unknown short-lived intermediate.[26] The mechanism of aneugenicity appears to differ from the clastogenicity with 2-chlorobenzaldehyde being the important metabolite regarding aneugenicity but not in respect of clastogenicity.[29]

In vivo studies

22. Negative results were consistently obtained in bone marrow or peripheral blood assays for micronuclei induction using high dose levels and both the oral and intraperitoneal routes.[23,33] (These assays are capable of detecting clastogens and aneugens if the active metabolite reaches the bone marrow.) It was noted that no data were available to indicate if adequate amounts of CS or short lived reactive metabolites reached the target organ. Data from DNA binding studies in the liver and kidney did not help in this regard as no relevant analysis of tissues of initial contact (ie skin or nasal mucosa) were undertaken.[21] Studies using Drosophila (fruit flies) did not provide any meaningful data as the experimental design was unlikely to result in exposure of Drosophila to biologically active CS.[23] It was felt prudent for complete reassurance on the lack of mutagenic activity of CS in vivo to have data from a study to investigate genotoxicity to measure potential mutagenicity at a site of contact, for example in the nasal mucosa. However, some members of COM recognised that the design of such an animal study would be difficult both from practical and ethical standpoints and were of the opinion that these studies were not necessary.

Carcinogenicity

23. The carcinogenicity data on CS were considered by the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC). Their conclusions are given in the following paragraph.

24. The US National Toxicology Program carcinogenicity studies provide no evidence that CS had any carcinogenic effects in adequately conducted inhalation bioassays in rats or in mice following 2 year exposure at up to 0.75 mg/m3 and 1.5 mg/m3 respectively.[20] These data provide reassurance that CS does not have mutagenic activity in vivo at site of contact tissues, a concern raised by the COM. No further work relating to CS is therefore needed in this area.

Reproductive toxicity

25. Developmental toxicity (teratogenicity) studies using the inhalation route and an aerosol of CS (1-2 µm mass median diameter) did not indicate any teratogenic or foetotoxic effects in rats or rabbits exposed to 60 mg/m3 CS (5 minutes per day) on days 6 to 15 of pregnancy.[34] Similar results were obtained when CS was given by the intraperitoneal route at 20 mg/kg as a single dose on day 6, 8, 9, 10, 12 or 14 of pregnancy.

26. There were no data available relating to single or multigeneration reproductive toxicity studies.

Effects in humans

27. Most of the data available relates to studies involving CS smoke or aerosol and exposure via inhalation. Aerosols were generated by thermal dispersion (particle size about 0.5 µm) or from a solution in methylene chloride (particle size about 1 µm). Studies on volunteers indicate that exposure to about 0.5 to 1 mg/m3 CS for 90 minutes in an exposure chamber produced profuse tears (lachrymation), involuntary repeated closure of eyes (blepharospasm), a burning sensation in the mouth, nasal irritation and symptoms of tightness in the chest; in some cases difficulty in breathing was experienced, particularly upon initial exposure.[35,36] Subjects were able to tolerate exposure at these levels throughout the 90 minute duration of this experiment. In general exposures of about 2.5 mg/m3 could be tolerated only for a few minutes. These data relate to subjects not previously exposed to CS. There is evidence for the development of some tolerance if exposures are built up slowly with 7/8 (88%) subjects then being able to tolerate 2.5 mg/m3 for 60 minutes.[36] Once exposure ceased all symptoms and signs, apart from headache, disappeared within a few minutes. No biologically significant effects were seen on respiratory function, blood chemistry nor in the pattern of electrocardiograms (ECG). However, the observation of effects on the ECG would be very dependent on the time after exposure at which they were measured and it is not clear from the published paper how long a delay occurred after exposure had ceased.[36] Dermal exposure of volunteers, by body drenching whilst only lightly clothed, with very dilute aqueous solutions of CS (up to 0.0005% w/v) resulted in marked transient skin and eye irritation.[37] During this period a rise in both systolic (30 to 59 mm Hg) and diastolic (15 to 30 mm Hg) blood pressures was noted

which took 2 to 25 minutes to fall to within 10 mm Hg of the controls. This was not dose-related and was not exacerbated by exercise.

28. Data from volunteer studies and experience in use, both in the manufacture of CS and its use in riot control, indicate that CS itself is a skin irritant. Volunteers whose forearm skin was exposed to dry powder experienced a mild, transient skin reaction.[38] The effects were more pronounced if the powder was moistened, when erythema lasted for between 1 to 2 days. Studies have also been carried out on volunteers whose forearm skin was exposed to high concentrations of CS under simulated tropical conditions.[39] Marked irritant effects could be produced although there was much variability in response depending on the individual and on local conditions (heat and moisture). A high incidence of dermatitis on the arms and neck has been reported at the industrial site in the USA that manufactured CS in the past.[39] Occupational hygiene standards at this plant were poor, with airborne CS concentrations of levels up to 12 mg/m^{3} (much greater than the Threshold Limit Value TLV* at the time of 0.4 mg/m^{3}).

29. Skin problems were common in individuals exposed to CS from grenades when these were used in Hong Kong during rioting at a Vietnamese detention camp, under circumstances where the rioters were not able to disperse.[40,41] A subsequent review of case records of 184 patients with symptoms consistent with CS exposure revealed a high incidence (52%) of skin problems including contact dermatitis and minor burns, most of which resolved within 2 weeks. Some of the skin injuries were caused by contact with hot canisters or grenades.

30. There is some evidence that CS can also produce skin sensitisation. At the CS manufacturing site referred to in paragraph 28, 8% (2/25) of the individuals who were patch tested with CS showed skin reactions consistent with allergic contact dermatitis.[39] There are also case reports of CS-induced allergic contact dermatitis in four individuals who were also exposed to CS from tear gas grenades.[42-44] There is, however, no information on the sensitisation potential of CS in solvent formulations.

* Threshold Limit Value (TLV): Occupational exposure limit, for an 8 hour time weighted exposure, recommended by the American Conference of Government Industrial Hygienists in the USA.

31. Data on eye irritancy are available from studies in volunteers. Exposure of young male volunteers to 0.1 or 0.25% CS as a slurry in 0.5% polysorbate, either directly (0.25 ml drop) or as a spray (hand-held disperser from 15 feet), resulted in a severe pain response for a few minutes, profuse tears and redness of the conjuctiva for about 10 minutes.[45] Comparable effects were seen in volunteers exposed to up to 1% CS in an organic solvent (trioctyl phosphate) using identical methodology.[46] There was complete recovery after about 30 minutes. Similar effects were seen in volunteers exposed to CS powder (0.8 μm mass median diameter) at up to 6.7 mg/m^{3} for 10 minutes.[47] There were no effects on visual acuity several minutes after exposure ceased. Data from experience in use indicates similar effects with transient pain, profuse tears and conjunctival reddening. There is no evidence from these studies of any permanent damage.

32. The question as to whether subjects being treated with neuroleptic drugs are likely to be more sensitive to CS spray has been raised.[48] There are no

experimental data to allow any conclusions to be drawn on this aspect of the toxicity of CS.

33. The only data on the effects of repeated exposure to CS derived from case reports of workers occupationally exposed.[2] These do not indicate any effects other than local irritant effects seen after acute exposure, but no conclusions can be drawn from these very limited data.

Toxicity of MIBK

34. MIBK is readily absorbed and widely distributed in various tissues of rats and mice following oral or inhalation exposure.[49,50] The major metabolites in rodents are 4-hydroxy-4-methyl-2-pentanone (4-OHMIBK) and 4-methyl-2-pentanol (4-MPOL) which may be further conjugated, or metabolised and eliminated as carbon dioxide, or incorporated into tissues.[50,51] Data on elimination of MIBK are incomplete. Studies in humans suggest that absorbed MIBK is rapidly cleared from blood and that very little unchanged MIBK is eliminated in the urine.[52]

35. Studies using hens have indicated that MIBK has the potential to induce microsomal metabolism carried out by cytochrome P450 enzymes in the liver after repeated exposure for 3 months. MIBK would thereby potentiate the effects of other chemicals (including drugs) that undergo activation via cytochrome P450-mediated metabolism.[53] These data, however, derived from studies involving prolonged, repeated exposure and are not relevant to single exposure, as is the case in the use of CS spray in the field.

36. MIBK is of low acute toxicity in rats or mice both by inhalation (4 hour LC_{50}* circa 12 g/m3) or by ingestion (oral LD_{50} circa 12 g/m3) or by ingestion (oral LD_{50} 2 to 5 g/kg b.w.).[54-56] Studies in rabbits to investigate skin irritancy using an occlusive dressing and 10 to 24 hour exposure resulted in minor transient effects, indicating that MIBK has a low skin irritant potential.[57,58] Repeated exposure produced drying and flaking of the skin due to the defatting action of MIBK. Eye irritancy studies in the rabbit using neat MIBK (0.1 ml) resulted in transient effects.[54] These results indicate that MIBK has low eye irritant potential.

* LC_{50}: Lethal concentration estimated to result in deaths of 50% of the exposed animals.
LD_{50}: Lethal dose estimated to result in deaths of 50% of the exposed animals.

37. Repeated dose (90-day) studies by inhalation showed effects on the liver and kidneys.[59] In mice the only effect seen, apart from lachrymation, at the top dose (4100 mg/m3) was a small increase (11%) in liver weight, not accompanied by histopathological abnormalities. A similar effect was seen in the liver of rats. In addition, nephrotoxicity was seen in the proximal tubules of the rat kidney at concentrations of 1025 and 4100 mg/m3 of MIBK. Nephrotoxicity was limited to the male rat and was associated with hyaline droplet deposition. It may have been due to binding to alpha-2 urinary microglobulin, a male rat specific protein; this mechanism is believed to be specific to the male rat.[60] The NOAEL was 205 mg/m3 in the rat and 1025 mg/m3 in the mouse.

38. In an unpublished 90-day oral study in the rat, histological evidence of kidney damage was reported at doses of 250 mg/kg and above, both in male and female

animals. There was increased liver weight, not accompanied by histopathological damage, at 100 mg/kg.[61] The NOAEL for this study was estimated to be 50 mg/kg.

39. There is no evidence that MIBK or its major metabolite 4-OHMIBK have any genotoxic properties. Negative results were obtained with MIBK in the Salmonella assay, a metaphase analysis for clastogenicity in hepatocytes, a mouse lymphoma assay, an unscheduled DNA synthesis (UDS) assay in hepatocytes and also in vivo in a bone marrow micronucleus assay.[62,63] Negative results were obtained for the metabolite in the Salmonella assay and metaphase analysis in hepatocytes.[62]

40. The developmental toxicity (teratogenicity) of MIBK in rats and mice has been assessed following exposure between 300 and 3000 ppm by inhalation on gestation days 6-15.[64] Maternal toxicity and foetotoxicity were observed in both species at 3000 ppm, but not at 1000 ppm. Significant reductions in foetal weight and ossification in the rat at 300 ppm were probably related to litter sizes and were not treatment-related. Contrary to the statement in some reports (which have relied on secondary sources and not the original article), there was no evidence of teratogenicity in either species, even at the maternally toxic exposure concentration of 3000 ppm.

41. It was noted that no carcinogenicity bioassays nor any single or multigeneration reproductive toxicity studies have been carried out on MIBK.

42. The characteristic effects noted in humans relate to local irritant effects and nonspecific central nervous system (CNS) effects (eg headache, nausea) at occupational exposures of about 100 ppm and above.[52,65,66] The odour threshold is low (0.4 ppm) and the irritant effects can be detected at about 2 ppm.[67]

Data on the combination of CS and MIBK

43. The Committee noted the sparsity of data on the combination of CS dissolved in MIBK. There are no data available on the metabolism, kinetics, acute toxicity, or skin irritancy of CS when administered in MIBK as solvent.

44. The only experimental data specifically on this combination consist of a study on the eye irritancy of 7% CS in MIBK (w/v) in rabbits.[68] This indicated that spraying 7% CS directly into the eyes of rabbits from close range produced severe irritant effects, including a degree of corneal opacity, which had cleared by day 8 and was not followed by irreversible damage.

45. Information was available from experience arising from the use of the spray from studies carried out by NPIS London Centre and the CIRS.[69,70] These indicated that there were cases of dermatitis following the use of CS spray: the effects produced were noted 6 hours after the exposure. No longer term follow-up studies have been carried out. There are also case reports of marked dermatitis following the use of CS spray in France. The report describes eleven subjects of whom five had multiple exposures to CS. The authors considered that a direct irritant effect was responsible, although an allergic dermatitis could not be ruled out. It is not clear from the published information whether exposure was to CS in MIBK or to

another formulation. In addition, no information is available on the ethnicity of the exposed individual who developed dermatitis.[71]

Worthington and Nee (1999) reviewed the clinical effects and management of CS exposure.[26] Serious potential ocular sequelae were stated to include glaucoma, cataracts, vitreous haemorrhage and traumatic optic neuropathy (Gray 1995). Other serious sequelae mentioned included chemical pneumonitis / pulmonary oedema, exacerbation of pre-existing asthma or chronic obstructive pulmonary disease, reactive airways dysfunction syndrome, chemical burns, and allergic contact dermatitis.

Karalliedde et al (2000) reviewed the immediate and long-term health effects following exposure to chemical warfare agents.[27] CS was stated to cause erythematous dermatitis and allergic contact dermatitis with vesicles, blisters, and crusts. The onset was noted to be between 12 hours and 3 days after exposure.

The Seattle and King County (US) Public Health website included information on riot control agents ie pepper spray and CS (2000).[28] It noted that for most people, any health effects from CS or pepper spray improved quickly and no future health problems would be expected. It did say that more severe health effects have been seen when people remain in an enclosed space where CS was present. In these cases exposure was for up to an hour or more and the concentrations were much higher than seen in outdoor air. It also noted that after exposure to CS, some people could have more severe skin reactions with a second exposure, namely, allergic contact dermatitis. It stated that there was no evidence that exposure to CS or pepper spray caused birth defects.

The Scientific and Technological Options Assessment Panel of the European Parliament produced a working document on Crowd Control Technologies (2000), including chemical irritants.[29] In appendix one of the technical annex, it listed that manufacturers, suppliers or distributors of chemical irritants numbered 88 in Europe, 7 in central / east Europe, 10 in Africa, 27 in Asia / Pacific, 12 in Latin America, 11 in Middle East and 113 in North America. This report provided information on chemical irritants including CS and discussed health effects. Relevant sections of the report are reproduced as follows:

> *The study questions the wisdom of maintaining the status quo where government and company research, often undertaken after chemical irritant weapons have been authorised, continues as the main approach to justifying alleged 'harmlessness.' Given that different countries even within the EU have adopted*

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[26] Worthington E, Nee P (1999). CS exposure - clinical effects and management. J Accid Emerg Med 16: 168-170. ID 27809

[27] Karalliedde L, Wheeler H, Maclehose R, et al (2000). Review article: possible immediate and long-term health effects following exposure to chemical warfare agents. Public Health 114: 238-248. ID 27810

[28] Environmental health hazards - riot control agents (2000). Seattle and King County Public Health. http://www.metrokc.gov/health/hazard/riotcontrol.htm. Accessed 12/12/2002. ID 26478

[29] OMEGA Foundation (2000). Crowd Control Technologies. Working Document for the STOA Panel. G. Chambers (Ed). Published by European Parliament Accessed at http://www.europarl.eu.int/stoa/publi/pdf/99-14-01-a_en.pdf.

different stances, there is a risk of not having proper regard to health and safety concerns, since many problems with toxic chemicals only emerge many years after operational usage. Both citizens and officers could have a future legal claim if scientific assertions of safety were later found to be less than well informed or negligent.

Likewise, in the case of French CS sprays, a failure to carry out adequate quality control meant that concentrations of the irritant chemicals were far in excess of the technical specifications.

2.1 Chemical Crowd Control Weapons - Design & Effects. Disabling chemical weapons used for law enforcement consist of a disabling chemical and a dispersion mechanism. There are inherent difficulties inevitable in marrying a chemical which has high effectiveness at very low doses with the requirement of low toxicity. Intensive work began in the 1950's, particularly in the USA and the UK, who shared their information on Chemical & Biological Weapons (CBW). In 1956, the UK War Office established the need for a chemical weapon able to drive back "fanatical rioters" which led to the adoption of CS, (then code numbered T792) for use in the colonies of Cyprus and British Guyana. In 1958, a Task Group on CBW was set up in the USA. The US Chemical Corps recommended two CW agents for consideration, namely CS and the vomiting agent DM, whilst describing mustard gas as "primarily a non-lethal agent."29 Work also began on searching for chemical incapacitants "particularly 'non-lethal' persistent chemical agents that are capable of attacking through the skin and can produce incapacitation for one to three weeks."30

Nowadays, the Chemical Weapons Convention permits the use of 'tear gas' and other toxic temporarily disabling chemicals and their precursors for law enforcement and domestic riot control purposes (which it does not define) as long as the chemicals listed in Schedule 1 of the convention are not used.31 This provision rules out DM, which is a toxic arsenic based substance previously held by certain countries outside the EU, including South Africa, which secretly explored the use of MDMA (Ecstasy) as a crowd control incapacitant.32

2.1.1 Disabling Chemical Irritant and Harassing Agents. By the 1970's, 15 different chemicals with sensory irritant properties had been reported for use in civil disturbances.33 However, despite intensive research,34 only four chemicals are commonly used for crowd control purposes, namely CN (1-chloroacetophenone), CS (2-chlorobenzylidene malononitrile), CR (dibenz (b:f)-1:4 oxazepine), and OC (Oleoresin Capsicum). Until recently, the two former agents were the ones most likely to be found in European police arsenals but increasingly European security forces are introducing OC. Whilst CR is usually a special forces weapon, although one company in India has packaged it for crowd control operations.35 In the Nineties, various US companies started to aggressively promote the use of Oleoresin Capsicum (OC) - a plant toxin extract derived from hot chilli peppers and therefore popularly known as 'pepper-gas' and later a more standardized synthetic variant emerged, known as PAVA (Pelargonic Acid Vanillyamide).36

CN was first prepared by Graebe in 1871 and like most so called 'tear gas' weapons is a solid which becomes a fine mist of particles when distributed. Thus technically speaking, the riot control agents are not gases but aerosols. In concentrations of about 10 mg/m3 it produces burning or stinging sensations in the throat, eyes and nose accompanied by excess salivation and profuse crying. It also causes exposed skin to sting and constricting sensations in the chest. In high concentrations this riot agent kills. It has a very low vapour pressure and is therefore persistent, contaminating room areas, vehicles, clothing and furniture all of which will require decontamination if untoward biomedical implications are to be avoided.

CS was first synthesized in the US by Corson and Stoughton in 1928 and is up to 5 times more potent than CN (based on the concentration per cubic metre that would be intolerable to 50% of an exposed population (ICt50) see Table 1), with marked harassment at concentrations of 4mg/m3. CS causes a burning sensation in the eyes which may be severe enough to precipitate involuntary eye closure (blepharospasm). It also produces severe irritation of the respiratory tract, burning pain in the nose, sneezing, soreness and tightness of the chest with coughing bouts following initial exposure and is a primary irritant of the skin. Even very light exposures can cause a rapid rise in blood pressure and as this increases, these effects become more intense with gagging, nausea and vomiting. A temporary fear of light, or photophobia is an associated side effect which occurs in roughly 10% of the people exposed.

CR was first synthesized by Higginbottom and Suchitzsky at Salford College of Technology (UK) in 1962 and is even more potent being six times more powerful than CS and 30 times more powerful than CN. It does not hydrolyse (i.e. split up or breakdown in water) which means that it can be dispersed from water cannon. The effects are mainly upon the eye and skin with the most severe effect on exposed mucous membranes. Concentrations as low as 0.01 -0.1% (0.1-1mg CR/ml) when splashed onto the face result in immediate eye pain and temporary blindness which persists for about 15-30 minutes. Over all areas of exposed skin contact, a nettle stinging sensation is produced which grows more severe as exposure increases. Even after a person is removed from the contaminated area, these effects will persist. Other effects include raised blood pressure, inner eye pressure, and, because of the general shock of the effects upon some individuals, hysteria.

OC is a mixture of extracts from the chilli pepper family, the exact constituency of which varies depending on the identity of the particular crop of pepper chosen to manufacture the OC product. PAVA is a synthetic formulation of one active OC constituent (known as capsaicinoids) which has been standardized to a specific level of irritant activity, measured in Heat Scoville Units (HSU) which register the relative level of heat inducing power. OC is the most potent of all of the commonly available riot control irritants although the ICt50 is unreported. OC and PAVA are classified as inflammatories, causing acute burning and closing of the eyes, along with severe inflamation of the mucous membranes and upper respiratory system. OC causes temporary blindness and uncontrollable coughing fits as the rapid inflammation of the respiratory tract restricts breathing. Being an organic agent,

OC is usually mixed with a carrier agent for dispersion, normally an oil, alcohol or kerosene etc.

2.1.2 Delivery & Dispersion Mechanisms. There are essentially two ways of delivering chemical crowd control agents either by a pyrotechnically delivered aerosol or as a sprayed solution. Many hand thrown cartridges are available consisting of a fused primer, irritant and a pyrotechnic ejection charge which delivers a dense cloud of irritant smoke. Some varieties fragment, others eject the chemical via a number of pierced holes in the container body. Manufacturers have also produced varieties which 'jump' across the ground erratically to avoid being thrown back. Micro-pulverised versions of irritants such as CS1 and CS2 are available for more effective dispersal via blast grenades such as the ISPRA 404D. Special barricade penetration devices such as Mace International's Ferret, have been designed to pierce doors, cars, plate glass windows etc, from a range of 100 metres.

Many pyrotechnic chemical irritant grenades are designed to be fired from both standard adapted conventional rifles or from a variety of 37/38mm multipurpose riot guns. Bulk distribution has been facilitated by manpack devices such as the Manroy mist sprayer which can spray up to two kilograms of specially formulated micronised CS at a rate of 300 grams per minute with a range of up to 17 metres using a 14 kg. two stroke engine.

The other main method of delivery is by a 'fly-spray' type cannister consisting of the irritant dissolved in a solvent with a propellant under pressure which is used to eject the chemical via a spray-nozzle, delivering either a cone of spray or a direct and targetable stream. CN, CS and OC can all be delivered this way via a variety of solvents and propellants. SAE Alsetex's CS sprays for example, use a 5% solution of CS in the solvent MIBK (methyl iso-butyl ketone). Other U.S manufacturers such as Advanced Defense Technologies and Federal Laboratories use the solvent methylene chloride. Zarc International quantify their spray delivery of capsaicinoids at 43,000 - 1,300,000 micro grams, per burst and is capable of a range of between 4.5 - 300 metres depending on the product. Many of the manufacturers of spray cannister chemical irritants also produce bulk delivery crowd control versions. Increasingly, manufacturers are fitting chemical irritant delivery systems to their internal security vehicles, helicopter and aircraft. Purpose built chemical irritant packs for water cannon are now appearing on the market.37 The cannon operator just adds the pack to the water cannon tanks for a specific concentration of chemical.

4.1.1 Hazards of Crowd Control Chemicals are associated with the way chemical irritants enter the human body via skin, lungs, mouth, nose and eye. To assess whether the epithet 'safe' can be applied to the currently authorised chemical crowd control irritants, it is worth examining the biomedical research literature used to justify their introduction, particularly in regard to lung and eye damage, carcinogenicity, mutagenesis, effects on heart rate, positional asphyxia and alleged 'non-lethality'. Experts on chemical warfare refer to safety margins i.e. the ratio of the lethal to the incapacitating dose. This is a finite measure. If it is surpassed, deaths will occur. However such agents are capable of producing a range of permanent injuries and such considerations are legally important when

the targeting of the irritant is less than discriminate and innocent bystanders fall prey to any effects.

CN has always been associated with potential hazards particularly in regard to its effects on skin and eyes, which provided the impetus to find a standard replacement. It was found to be between 3 and 10 times more toxic than CS in rats, rabbits, mice and guinea pigs.78 (See Table 1). It creates more severe damage to the lung with more edema, patchy acute inflammatory cell infiltration of the trachea, bronchi and bronchioles and more evidence of early bronchopneumonia.79 Very early on it was noted that CN can induce primary irritant dermatitis.80 In skin tests it was found CS caused no effects below 20 mg, whereas moist CN caused vesication (blistering) in most subjects.81 It is also a more potent skin sensitizer than CS82 with several people developing allergic dermatitis.83 CN has also been associated with longer lasting burning of the cornea84 and even permanent eye injuries,85 particularly if the irritant has been propelled into the eye at short range.86 In higher doses it is lethal,87 particularly in enclosed spaces where even one 128g grenade in a 27 m3 room, is sufficient to kill.88

CS - There is extensive scientific literature on CS, one recent search claims to have found 115,107 articles.89 Only some of the most salient aspects can be discussed here. Advocates of CS claim that high levels of exposure to CS are precluded because people are adverse to remaining where this agent is present.90 More critical authors have noted the lack of epidemiologic inquiry on its use in actual field conditions.91 However, operational usage sometimes means individuals face additional punishment or even death if they seek to leave a contaminated zone. (See examples in Appendix 6). At higher levels of exposure, inhalation toxicology studies indicate CS can cause chemical pneumonitis and fatal pulmonary edema. (Victims die by drowning in their own lung fluids).92 CS exposure can also lead to reactive airways dysfunction.93 Oral toxicological studies note the facility of CS to cause severe gastroenteritis with perforation.94 CS is a primary skin irritant and some individuals will develop contact dermatitis even after what appears to be an unproblematic initial exposure and severe blistering can emerge several hours later.95 An exposure to even a low concentration of CS raises blood pressure and there is a particular risk of health damage to anyone over 30, under physical strain or having an undetected aneurysm.96 At higher levels CS has been associated with heart failure, heptacellular (liver) damage and death.97 98 One US based CS manufacturer, Federal Laboratories, has warned that "Firing one Federal No. 230 Flite-Rite [tear gas projectile] in a room [eight-feet by eight-feet by seven-feet], could endanger the life of an average subject if he stayed in the room for seven minutes".99 CS from canisters has also caused acute mass chemical burns.100 (Figure 5 illustrates the severe blistering following exposure to French CS Spray).

In vitro laboratory testing has shown CS to be clastogenic, (i.e. causes disruption of chromosomes) and mutagenic (ie it has a facility to cause inheritable genetic changes in organisms).101 Other studies have shown CS to cause an increase in the number of abnormal chromosomes.102 The risks of a build up of exposure are increased because of the acquisition of tolerance to CS.103 This tolerance is stronger in those of higher commitment and or intelligence104. One military study on the carcinogenicity (cancer causing) potential of CS was inconclusive but

observed that chronic exposure to very low concentrations of CS is of greater concern and should be further studied.105 This is an important safety consideration for police officers who may be regularly exposed to cross contamination when using CS which is particularly persistent. Military CS1, a micronised powder version (and CS2 - a siliconized,micro-encapsulated version of CS1) are even more persistent and therefore form an environmental clean up hazard.

CR - is normally restricted to special operations units, like the SAS, engaged in anti-terrorist operations. Only one EU member State, the UK is definitely known to hold stocks. However, when the relevant Home Office department was asked by researchers about its holdings of this agent, it simply omitted data which in fact was already in the public domain.106 Whilst a range of studies have been presented to suggest that CR is less toxic and more potent than CS or CN,107 (See Table 1) there are no operational case studies, only military studies on human volunteers.108 These studies found that CR increased blood pressure and anxiety and later studies asserted that there was significantly less risk of eye damage than with CN and CS109, neither was CR teratogenic (the facility to cause congenital foetal abnormalities, ie birth defects).110

In the UK, the real significance of CR was as a test case for the Himsworth recommendations following the massive use of CS in Northern Ireland. Himsworth said that in future riot agents should be treated more as drugs with full reporting of the data justifying assertions of safety in the open scientific press before they could be authorised for use.111 Despite assertions that it followed Himsworth's recommendations, the UK Government failed the test - when asked about studies used to justify claims that CR was not mutagenic or carcinogenic, it quoted studies published several years after authorisation had been given.112

For legal reasons, it is difficult to think of a drug that would be given the go-ahead in such circumstances where the biomedical effects had not been properly evaluated before the drug goes on to the market. Yet given the Health and Safety implications of the use of chemical irritants (not only on those targeted but on the police and security officers who may be exposed on a regular basis) it is important that these biomedical effects are understood and analysed, as if these chemical irritants were in fact new drugs. For reasons of public safety, this report suggests that such studies should be a legal requirement. Then any assertions of safety and less-lethality can be properly defended in a court of law, so that in the future should such assertions prove untrue, it is possible to firmly establish where culpability lies, either with the manufacturer or with the operator.

OC & PAVA An earlier STOA Report (PE 166.499) covered the alleged hazardous health effects of Peppergas particularly for those with asthma, taking other medical or recreational drugs or subject to restraining techniques which restrict the breathing passages posing a risk of death. The Los Angeles Times reported at least 61 deaths associated with OC since 1990 in the US and there have been more since.113 Much of the disquiet was associated with the corruption which took place in regard to the FBI approval of this chemical irritant for police use. FBI special agent Thomas WW Ward was later prosecuted for taking a kickback of $57,000 from a pepper gas manufacturer. Claims that OC was mutagenic and a

neurotoxin were later rejected by the US Marines.114 However for a period afterwards the Marines restricted field training with the irritant because of worries about its safety. US police are enthusiastic about the alleged 90% effectiveness of this irritant in incapacitating humans and reducing injuries to officers.115 It is easy to understand the need for such an aggressive alternative in the highly armed context of the US. In Europe however, it may be wiser to be more circumspect especially given the need to medically supervise anyone who has been sprayed with peppergas. The previous STOA report advised the European Parliament to err on the side of caution and called for a moratorium on the acquisition, sale and deployment of Oleoresin Capsicum irritant sprays, until independent research is undertaken on its safety and published in full in the scientific press for peer review. Such work is beginning. For example in the Netherlands,116 the UK and in Sweden. However, different EU States have reached different conclusions, for example Sweden has refused to adopt the agent, partially because of research findings that there was a risk of severe damage to the cornea.117 These findings are consistent with those of researchers in North Carolina (USA) which report that capsicum is mutagenic, leads to degeneration of nerve fibres in the cornea with associated neuroparalytic keratitis (manifested by corneal edema), brain and nerve damage, liver damage, an increase in peptic ulcer disease and kidney damage. Stopford also stated that there was a range of medical risks associated with the use of OC spray including eye damage; skin blistering and allergic dermatitis; laryngospasm (constriction of breathing passages) and respiratory arrest (with asthmatics being more sensitive with up to 40% decrease in air flow compared to health individuals); pulmonary oedema (fluid in the lungs - the risk of which significantly increases with prior infection); airways reactivity and broncho-spasm; hypertensive crisis leading to acute elevation of blood pressure and hypothermia.118

There are also contradictory positions on PAVA (the synthetic OC irritant) between different EU states. Whilst IDC of Freienbach, Switzerland, the key European distributer of PAVA (with 18 European patents119) claims its PAVA products are both safe and legal in Switzerland, Austria, and Germany, the UK position is that the "Home Office Police Scientific Development Branch considers the information currently available is not sufficient to allow the use of PAVA as an incapacitant in the United Kingdom at present".120 However, Civil Defence Supply Ltd has been awarded 45,000 from the UK Department of Trade and Industry to research PAVA as an allegedly safer alternative to CS to become what the company hopes will be the 'incapacitant for the millennium.'121

Finally, in regard to safety, it is worth recalling that way back in 1975, the Stockholm International Peace Research Institute was warning about delayed toxic effects from chemical warfare agents including tear-gases.122 Not all the effects of using these chemicals will emerge straight away and just as the full implications of tobacco and asbestos only became apparent many years after their popular usage, so might be the case with chemical crowd control agents. Given the overall costs of litigation associated with tobacco and asbestos, it is worth reminding ourselves that the precautionary principle pays off in the longer term.

4.1.2 Hazards of Dispensing Excess Levels of Chemical Irritant There are many instances of the police and the military using CS either excessively or

indiscriminately. For example, the South Korean government admitted to using 351,000 canisters and grenades of CS throughout the major cities, in June 1987.123 There are reports of demonstrators passing out or experiencing heart attacks during episodes where helicopters were used to spray teargas.124 No official scientific studies on the biomedical impacts of this CS barrage on the health implications for those working in Seoul, including the police themselves appear to have been published either then or since.125 However, in 1999 the South Korean authorities in Seoul announced a policy of not using CS as a crowd control option. (See Section 7).

When such indiscriminate mass sprayings involve different riot agents, the health risks are compounded. For example, severe health problems were reported in at the anti WTO protests in Seattle last December, where the police used a combination of CS,CN and OC.126 Even some of the manufacturers of these products warn about the synergistic consequences of such mixing "which can prove harmful or even fatal in real life situations". Zarc International also asserts that a mixture of CS with OC in pepper sprays has caused "documented eye injury and blindness".127

The issue of excessive delivery of agent to subject also touches on product design and actual adherence to technical specification. For example, in November 1996, a UK Channel 4 Dispatches programme found that the concentration of CS in UK sprays at 5%, was five times higher than similar sprays in the USA and the flow rate was also five times greater which means that anyone targeted in the UK would receive 25 times the amount of chemical irritant used in America.128 Even that figure may be an underestimate. An internal Home Office note suggests that the French manufactured CS sprays may contain an even higher concentration than the stipulated 5%. Spot checks carried out by one UK police force revealed concentrations of CS between 5.4 and 6.8 per cent, ie a CS "dump rate" of between 27 and 34 times that used in the USA.129 The Home Office has asked SAE Alsetex, which manufactures the spray, about their alleged failure to ensure product quality control in terms of the higher than stipulated concentrations. According to the note of February 1997, the company simply said that they had not been measuring the concentrations of CS in their canisters up to that point. The UK Home Office admitted that it had no system of regular spot checking these devices. When forces do undertake such an inspection the results are worrying. In December 1997 another force checked their canisters and found concentrations of 8.5 % or a "dump rate" of 42.5 times more than would be permissible in the USA.

Other hazards of excess application of chemical irritants are related to the development of tolerance. Such tolerance has been associated with people taking medication because of mental health problems and/or recreational drug users, factors which can diminish the effectiveness of the chemical irritants. Why tolerance occurs in these groups is unclear but it may be related to reduced anxiety.130 A recent report by the UK Police Complaints Authority has recommended that where mental illness is involved "that training should emphasise the risks involved in using the spray on those who are vulnerable through mental illness, alcohol or drugs, and that the [CS] spray may not work in these circumstances and may also exacerbate a violent situation" and "that training should reinforce the need for consultation with family and mental health

professionals where possible, to find alternatives to the spray as suggested in ACPO's 1999 guidance".131 However no guidance is provided on how mentally ill people are recognised at a distance.

The tolerance phenomena is proportionally significant. For example, in regard to CS, the UK Police Complaints Authority reported a failure of subject response at 18%.132 Cincinnati police in Ohio reported a 13% failure rate with CS and cited this as the main reason for testing OC products because of the manufacturers claims that it is effective on psychotics and persons under the influence of drugs or alcohol.133 However, analysis of the effectiveness of OC pepper spray in Berkeley contradicted this notion, reporting OC to be ineffective 35% of the time.134 Such tolerance has implications for dosage levels since it is experienced by the spraying officers as ineffectiveness or potency of their weapon. A common reaction to such a lack of impact is for officers to use more of the irritant. Often police guidelines contradict those provided by the manufacturers. A worrying example of the implications of such confusion regarding appropriate dosage is the Novato (California, USA) police case which led to the death of a man who was sprayed with OC. Novato police OC guidelines advise that suspects "shall not be exposed to oleoresin capsicum (pepper spray) for longer than absolutely necessary to accomplish control". John Crew, Director of the Police Practices Project for the ACLU of Northern California stated that, "this contradicts how the manufacturers say pepper spray should be used because it implies that you spray until the suspect is subdued... the manufacturers advise that if you hit the suspect's target area, and it doesn't work, it's not going to work, and improperly prolonged spraying poses a health risk to the suspect".135

Other hazards associated with excess dosage include delayed allergic contact dermatitis, the severity depending on the level of exposure136 - in some cases leading to vesication, the time course of which is the same as that for skin damage caused by exposure to mustard gas.137

4.1.3 Hazards of Carrier Solvents & Propellants can be illustrated by the case of French made CS sprays being prematurely introduced into the UK on 1 March 1996, before the requisite scientific research was accomplished. One of the key issues considered by the UK Department of Health Committee (subsequently set up to assess the product's safety) were the hazards posed by the solvent Methyl Isobutyl Ketone (MIBK) - used to dissolve solid CS so that it can be used as a targetable spray. Official reports show that government scientists have warned on at least two occasions that MIBK is too dangerous to be used in CS sprays. But the UK Home Office and Police Forces ignored both reports and continued using MIBK. Four years ago the Home Office commissioned scientists at Porton Down to compare the toxicities of MIBK and an alternative solvent methylene chloride.

In July 1996, the Porton scientists "strongly recommended" that the police should use methylene chloride, rather than MIBK in their CS sprays. Just a month before Home Secretary Michael Howard introduced MIBK based CS sprays, Porton Down was advocating that the available information would suggest that methylene chloride, in the vapour form, is likely to be less hazardous than MIBK.138 139 140 In addition, Porton Down was of the view that methylene chloride would pose a significantly reduced risk given that the current handheld spray containing CS

dissolved in MIBK delivers liquid droplets rather than solid particulate CS. This comment is significant because it raises questions about the controllability of the amount of chemical irritant and associated solvent dumped on the target. In the following year, Porton scientists were again commissioned by the Home Office to scrutinize 28 solvents to advise on one which would be both safe and effective in CS sprays. Again they concluded that MIBK was 'a serious hazard' and put it into a group of chemicals which were 'clearly' not safe solvents because they were "either confirmed or suspected carcinogens with associated mutagenic potential." This time, the Porton Down scientists' considered advice was that for a definitive answer on a low toxicity solvent for CS spray devices the properties of di(propylene) glycol and polyethylene glycol should be investigated.141 As before, this report was brushed aside in a way which would be politically and legally unforgivable if these substances were drugs rather than riot control agents. Yet the UK Committees on Toxicity, Mutagenicity and Carcinogenicity gave the product the all clear despite noting "the sparsity of data on the combination of CS dissolved in MIBK".142 The UK Police Complaints Authority report already referred to has also advised that research should be progressed rapidly on finding alternatives to the solvent MIBK.

4.1.4 Hazards Of Pyrotechnic & Blast Chemical Irritant Delivery Systems. Blast injuries from fragmentation devices are far from uncommon. The fact that pyrotechnic devices are incendiary creates both a risk of burn injuries and the initiation of a fire. For example 96 cases of acute burn injuries were reported when teargas was used against refugees in a Hong Kong Detention centre.143 The Material safety sheet on CS assigns a flammability rating of 4 (on a scale 0-4) and some commentators now ascribe incendiary CS grenades as a large contributor to the conflagration which burned the Branch Davidian Compound and its inhabitants at Waco, Texas, in 1993144.

4.1.5 Training & Professional Codes Of Conduct. The notion that such chemical irritants are 'nonlethal' is based on an assumption that they are used in accordance with manufacturers instructions and not in enclosed spaces. When disputes over appropriate usage occur, there needs to be a clear line of accountability. In Canada, when an innocent man was sprayed with pepper-gas and suffered injuries to his eyes and lungs he sued the local police because of the longer term effects (bronchial asthma and reactive airways dysfunction syndrome). The police officers in Ottawa defended the claim by filing a third party claim against the manufacturer Defense Technology (Def-Tec). However, the company claimed the fault was that of the police for failing to train its officers properly. The company alleged that "police negligently caused the product to be activated for an excessive period of time145."

In the UK, complaints about tear gas by members of the public have ballooned. In the year up to March 1998, the Police Complaints Authority received 425 complaints about the sprays compared to 254 in the previous year.

Fraunfelder (2000) in an editorial in the BMJ noted that CS particles become primarily attached to moist mucus membranes and moist skin.[30] The eye was considered to be the most sensitive to CS causing epiphora, blepharospasm, burning sensation, and visual problems. Other effects noted included coughing, increased mucus secretion, severe headaches, dizziness, dyspnoea, tightness of the chest, skin reactions and excessive salivation. Onset of symptoms occurred within 20 to 60 seconds, lasted usually only 10 to 30 minutes, if the subject was removed from the exposure. It was considered that the medical literature mostly supported the safety of CS but the author also noted that significant reactions had also been reported, but usually in association with excessive use or persistent exposure. The author noted that there was no scientific data available on the relative safety of 1% CS (used in the US) versus 5% CS (used in Britain). A report by the British Department of Health (1999) found that toxicity data was available for CS, less so for the solvent methyl isobutyl ketone (the solvent used with CS in Britain) and only limited data on the formulated product. The report concluded that 5% CS in methyl isobutyl ketone was not associated with major health concerns but long-term follow-up studies of exposed humans were needed, particularly potentially susceptible individuals with asthma, chronic obstructive disease, hypertension, cardiovascular disease, or those taking neuroleptic drugs. Blaho and Stark (2000) in reply to this editorial noted that CS was not a gas, but rather a particulate spray.[31] The introduction of CS in Tennessee by the police had not resulted in any significant injuries among exposed subjects or police officers. The most common persistent complaint was noted to be ocular irritation. Gray (2000) noted that the solvent used in the British formulation of CS was methyl isobutyl ketone, an industrial degreasing agent that removes lipid from skin, causing reddening, scaling, blistering, as well as ocular and respiratory tract irritation.[32] In the chemical industry, use of skin and eye protection was advised when handling MIBK. Jones (2000) considered that the recent report by the British Department of Health (1999) was disturbingly flawed.[33] He noted that repeated exposure to CS could result in contact allergic dermatitis and that the Report largely discounted the only report of the effect of the CS-MIBK formulation on humans where erythematous dermatitis, skin blistering and keratitis were described [Parneix-Spake et al 1993].

Hill et al (2000) reviewed the literature on the medical hazards of CS.[34] The authors noted that tear gases were widely regarded as free from serious or persisting toxicity under typical conditions of use and reports of illness from CS were scarce, apart from skin conditions. The mechanisms of action of CS involve alkylation of SH-containing enzymes [Cucinell et al 1971, Himsworth 1971, Jones 1972] and local formation of hydrochloric acid regarding skin and mucus membranes. The breakdown of CS produces cyanide but levels were considered minimal after inhalational exposure [Ballantyne 1977, Himsworth 1971]. CS has a very short half-life in the circulation [Himsworth 1971, Leadbeater 1973]. The acute clinical effects of CS involve irritant effects on the skin and mucus membranes, with an onset of seconds to minutes and lasting from 15 minutes to several hours. Delayed reactions, with an onset, hours to

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[30] Fraunfelder F (2000). Is CS gas dangerous? Current evidence suggests not but unanswered questions remain. Editorial. BMJ 320: 458-9. ID 23893.

[31] Blaho K, Stark M (2000). Re: Is CS spray dangerous? CS is a particulate spray, not a gas. BMJ 321: 46. ID 27419.

[32] Gray P (2000). Re: Is CS spray dangerous? Formulation affects toxicity. BMJ 321: 46. ID 27419

[33] Jones G (2000). Re: Is CS spray dangerous? Hazards are being hidden. BMJ 321: 47. ID 27419

[34] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.

days after exposure may occur with excessive doses. More serious injury was said to occur with excessive doses, exposure in an enclosed space, prolonged exposure, a high minute volume eg fight and when temperature and humidity are high (re skin). Acute symptoms include:

Eyes - lacrimation, chemical conjunctivitis, chemosis, blepharospasm

Skin - burning, erythema, burns with heavy exposure

Respiratory tract - burning in nose and throat, rhinorrhea, salivation, chest tightness, and cough

Other - nausea, vomiting, headache, photophobia, malaise, raised blood pressure

CS exposure can result in both irritant and allergic contact dermatitis [Anderson et al 1996, Fuchs 1990, Parneix-Spake et al 1993, Shmunes and Taylor 1973, Fisher 1970, Sommer and Wilkinson 1999, Ro and Lee 1991, Maibach and Marzulli 1971].[35] Allergic contact dermatitis has been seen after repeated low-level exposure among military, police and industrial workers [Kanerva et al 1994, Shmunes and Taylor 1973]. A delayed allergic dermatitis has been reported in several subjects from 5 days to two weeks after a single exposure, suggesting local persistence of the antigen [Kanerva et al 1994, Sommer and Wilkinson 1999]. It may be difficult to clinically differentiate between irritant and allergic contact dermatitis; patch testing is useful. Solvents used in the tear gas mixture have also been reported to result in both skin conditions.

Exposure to CS can lead to severe conjunctivitis and corneal lesions but no serious ocular injury or long term sequelae have been reported [Gray 1997, Leyland 1997, Willoughby et al 1998].[36] Particles from explosive delivery devices can also lead to ocular trauma [Hoffman 1967].

In experimental animals with prolonged inhalation of CS, lung injury was the main cause of death.[37] Pulmonary vascular congestion, with focal haemorrhages and oedema in severe cases, were the most consistent histological findings. With the occasional exception in monkeys, full recovery occurred in animals that survived the acute exposure. The authors noted that no case of CS-induced human lung injury had been documented pathologically. Studies on healthy human volunteers found no acute effect on the chest examination, lung mechanics or diffusing capacity after exposure to low-dose CS [Beswick et al 1972, Cotes et al 1972, Himsworth 1971, Punte et al 1963]. There were a few anecdotal reports of exacerbation of pre-existing airways disorders, especially asthma, after exposure to higher doses of CS [Anderson et al 1996, Breakell et al 1998, Fuchs 1990, Himsworth 1971, Hu et al 1989]. No reports of formal testing for airway hyperreactivity after CS exposure were found. There were two case reports of prolonged airway dysfunction (RADS) that commenced after CS exposure [Hu and Christiani 1992] and after combined CS and OC exposure [Roth and Franzblau 1996]. A further two unconfirmed cases after unrestrained use of CS were also mentioned [Fuchs 1990; Hu et al 1989]. The authors considered it likely that high-dose CS inhalation could cause life-threatening pulmonary oedema (ARDS)

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[35] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.

[36] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.

[37] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.

or airway lesions in humans [Chapman and White 1978, Himsworth 1971]. Only two reports of clinically apparent parenchymal lung injury were found. One subject developed suspected pulmonary oedema and a focal lung opacity, followed by pneumonia (? infectious) on day 13 [Krapf and Thalmann 1981]. The second report involved a 4-month old infant with acute respiratory distress and airways obstruction after prolonged exposure to CS. Secondary pneumonia (? infectious) developed 1-2 weeks after exposure [Park and Giammona 1972].

Major liver injury has not been reported.[38] Serum liver enzymes were not raised up to 24 hours after exposure to CS in a study of volunteers [Beswick et al 1972, Himsworth 1971]. Repeated low-dose exposure to CS produced no liver dysfunction in seven subjects [Punte et al 1963]. One case report claimed hepatocellular damage but the current authors considered that the laboratory data were not supportive of significant hepatitis [Krapf and Thalmann 1981]. Animal studies have observed non-specific hepatocellular necrosis but this was attributed to hypoxia [Ballantyne 1977, Ballantyne 1978, Himsworth 1971]. The authors considered that it was still uncertain, although plausible, that CS was a direct hepatotoxin.

The authors considered that human death as a result of CS exposure had not been authenticated, despite several suggestive anecdotes [Chapman and White 1978, Himsworth 1971, Hu et al 1989].[39] The authors concluded that there was a paucity of documented lasting effects despite the widespread use of CS for more than three decades. CS appeared safe when deployed outdoors in a controlled manner but it can cause important injuries if misused or if applied to a sensitised subject.

A fact sheet was produced by the US Department of Defence (2002), about the test, Cliff Rose.[40] The primary test objective of Cliff Rose was the evaluation of three CS weapon systems in tropical and semitropical environments. These CS weapon systems were evaluated in forest, open water (paddy), jungle, high grass, and open terrain, on unmasked walking test subjects. For this test, CS2 was dispersed by Air Force low- and high-speed tactical aircraft, burster devices, and an UH-1 type helicopter. The test Cliff Rose was conducted between September 22, 1967 to January 18, 1968, at Fort Stewart, Georgia (Phase 1) and at an unspecified location in the Panama Canal Zone (Phase II). Under potential health risks, CS2 was stated to be one of several chemicals commonly called "tear gas". CS2 is a white, crystalline powder and is dispersed into the air as either an aerosol or powder. The chemical name for CS2 is orthochlorobenzylidene malononitrile. It is chemically identical to CS but differs in its physical characteristics. This chemical is an incapacitating riot-control agent that acts as a contact irritant on the exposed body surfaces (eyes and skin), and on the respiratory tract. Exposure to CS2 causes burning, irritation, tearing and pain in the eyes. Airway symptoms include burning, sneezing, coughing, shortness of breath and increased secretions, such as runny nose and increased salivation. High concentrations of CS2 can cause blistering of the skin. With commonly used concentrations, these effects are short-term and the potential for long-term health consequences is low.

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[38] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.
[39] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.
[40] US Department of Defence (2002). Office of the Assistant Secretary of Defence (Health Affairs). Deployment Health Support Directorate. Deseret Test Center - Cliff Rose. ID 26477.

Greenfield et al (2002) discussed microbiological, biological, and chemical weapons of warfare and terrorism.[41] It was noted that tear gas was principally used for riot control and for subduing suspected criminals but has also been used in warfare. The gases most commonly used were chloroacetophenone and orthochlorobenzylidene-malononitrile. Tear gas produced profuse symptoms of eye, oropharyngeal and nasopharyngeal pain, rhinorrhea, and upper airway irritation. Heavy exposure inside enclosed structures has resulted in acute lung injury, acute respiratory distress syndrome and death.

Smith and Greaves (2002) reviewed the use of chemical incapacitant sprays.[42] They noted that the first large-scale review was conducted by Himsworth (1969), after the use of CS by the police in Derry. It concluded that exposure to CS could be potentially lethal as a result of toxic pulmonary damage leading to pulmonary oedema (on the basis of animal studies), but such an occurrence in humans would only occur at concentrations higher than those tolerable. They also noted that many of the concerns about the current use of CS in Britain centred around the solvent MIBK. MIBK was noted to result in irritation of the eyes and skin, dermal erythema, blistering that may appear up to eight hours after exposure and last up to a week. Regarding CS itself, more severe effects were said to include skin erythema, blistering and a more chronic allergic dermatitis. Reports were mentioned of laryngospasm, pulmonary oedema and reactive airways dysfunction syndrome with respiratory symptoms persisting for many months. However, there were no reports in the current literature of death directly attributable to CS exposure.

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[41] Greenfield R, Brown B, Hutchins J, et al (2002). Microbiological, biological, and chemical weapons of warfare and terrorism. Am J Med Sci 323: 326-340. ID 26445.
[42] Smith J, Greaves I (2002). The use of chemical incapacitant sprays: a review. J Trauma 52: 595-600. ID 27416.

Acute Effects - Human Volunteer Studies or Case Reports / Series

Owens and Punte (1963) conducted a trial of six male volunteers exposed to aerosols of chlorobenzylidene malononitrile of different particle size.[43] The subjects were exposed singly in a small wind tunnel at a constant airspeed of 5 miles per hour. Small particles of chlorobenzylidene malononitrile (median diameter of 0.9 microns) came from a 2% solution of the compound in methylene dichloride. Large particles of chlorobenzylidene malononitrile (median diameter of 60 microns) came from a spraying system using a powder. The eyes-only, respiratory system-only and eyes and respiratory system of subjects were exposed to either small or large particles. The airborne concentration of chlorobenzylidene malononitrile was 94 mg / cubic metre for small particles and 85 mg / cubic metre for large particles. Small particles were more effective than larger ones in producing eye irritation; 2/5 versus 6/6 subjects tolerated the exposure for at least 60 seconds when the eyes alone were exposed. However, it took subjects longer to recover after eyes-only exposure to large particles (280 seconds) compared to small particles (91 seconds). Small particles were also more effective than larger ones in producing respiratory effects; 0/6 versus 4/6 subjects tolerated the exposure for at least 60 seconds when the respiratory tract alone was exposed. It also took subjects longer to recover after respiratory system-only exposure to small particles (51 seconds) compared to large particles (9 seconds). When both the eyes and respiratory system were exposed, the response was mostly respiratory with small particles [1/6 subjects tolerated for longer than 60 seconds and it took 52 seconds to recover]. The response was mainly ocular for larger particles [5/6 tolerated for longer than 60 seconds and it took 188 seconds to recover]. The subjects admitted to the trial were selected [the six out of 50 volunteers who appeared best able to tolerate CS were chosen].

Punte et al (1963), from the US Army Chemical Research and Development Laboratory, reviewed the results of exposure of human volunteers to CS.[44] Volunteers with a history of hypertension, hay fever, drug sensitivity, bronchial asthma, hepatitis, or peptic ulcers were excluded. Each subject was interviewed and examined before, after and 2 to 4 days after CS exposure. Four to six volunteers were exposed at one time to the CS aerosol, in a wind tunnel at a fixed wind speed of 5 miles per hour. CS aerosol was dispersed from a 10% solution in methylene dichloride with a spray nozzle or by spraying the molten chemical (thermal dispersion). The response of subjects exposed to CS dispersed thermally was not different to that obtained in subjects exposed to CS in solvent. Hyperventilating subjects [n = 9], who ran about 100 yards, could not tolerate CS [10 to 39 mg per cubic metre] as well as normally breathing subjects. There was a slightly prolonged recovery time, in the range of one to two minutes. Eye symptoms were negligible but chest symptoms were pronounced. When higher temperatures were used [95 F, 35% and 97% relative humidity], subjects [n = 9] were unable to tolerate CS [8 to 40 mg per cubic metre] as well as subjects exposed at ambient temperatures, but the decrease in tolerance was not great. Skin symptoms were much more prominent. The ability to work in a CS-contaminated environment was tested in five subjects by measuring the time to complete 50 simple addition problems before, during and after exposure to a low concentration of CS [4-5

[43] Owens E, Punte C (1963). Human respiratory and ocular irritation studies utilising o-chlorobenzylidene malononitrile aerosols. Am Ind Hygiene Ass J 24: 262-264. ID 26782
[44] Punte C, Owens E, Gutentag P (1963). Exposures to ortho-chlorobenzylidene malononitrile. Controlled human exposures. Archives of Environmental Health 6: 72-80. ID 26680

mg per cubic metre]. The time to complete the problems was significantly longer during exposure to CS but this appeared to recover after the exposure ceased. Accuracy was impaired in only one subject who was unable to tolerate the CS cloud. Seven subjects exposed ten times to CS [1 to 13 mg per cubic metre] during a period of two weeks revealed no clinical abnormalities in serum electrolytes (sodium, potassium) or urinalysis (albumin, specific gravity) measured before and after exposure. There was no change in the liver function tests sulfobromophthalein and alkaline phosphatase measured before and after exposure and two months after exposure (only done for AP), apart from an elevation in thymol turbidity in one subject (measured before, after and two months after exposure). No subject developed noticeable tolerance to CS during these ten exposures. Four subjects were exposed to CS at 1.5 mg per cubic metre for 90 minutes. All developed slight nose and eye irritation that subsided during exposure and three of four subjects developed headaches that persisted 24 hours after exposure in two subjects. Four subjects were exposed to CS at 1.5 mg per cubic metre for 40 minutes and then the concentration was increased to 11 mg per cubic metre attained over 10 minutes. Within two minutes of this increase, all four subjects left the exposure chamber due to respiratory irritation. Four subjects were exposed to CS at 6 mg per cubic metre. Signs and symptoms were nose and throat irritation, chest burning, sneezing, eye irritation and tearing, headache, and skin irritation. Three of four subjects left the exposure chamber after 18, 20 and 19 minutes respectively due to chest effects. Four subjects were exposed to CS at a concentration of 6.6 mg per cubic metre attained over 30 minutes and which lasted 60 minutes. The usual signs and symptoms developed but to a lesser degree. Symptoms and signs were classified as either major or minor. Major symptoms consisted of ocular and respiratory affects. Ocular: Burning and pain in the eyes and conjunctivitis occurred immediately. The former persisted for two to five minutes but conjunctivitis remained intense for 25 to 30 minutes. Erythema of the eyelids was generally present and persisted for an hour and was occasionally accompanied by blepharospasm. Lacrimation persisted for 12 to 15 minutes. Photophobia was marked in 5% to 10% of subjects and remained up to an hour. Occasionally subjects complained of "tired eyes" lasting about 24 hours. Respiratory tract: Burning in the throat which then progressed down the respiratory tract, occasionally associated with coughing, followed by a feeling of chest constriction. Ausculation of the chest immediately after CS exposure never revealed wheezes, rales or rhonchi. The breathing pattern of exposed subjects involved involuntary gasping when the aerosol was inhaled, then breath holding or slow shallow breathing, followed by paroxysms of coughing. An irregular respiratory rhythm was noted for several minutes after CS exposure was ceased. Longer-term tests of respiratory function are discussed under the respiratory section. Minor symptoms consisted of burning of the nose and throat (ceased readily in fresh air), rhinorrhea and salivation (persisted up to 12 hours) and self-limited minor epistaxis (in several persons working with CS). Taste perversion for substances such as cigarettes and carbonated beverages (persisted for 30 minutes), nausea (alleviated by fresh air), no vomiting observed, diarrhoea observed in about 1% of subjects (severe in one subject and lasted for 8 hours), and eructation in six subjects lasting from one to seven days. Occasional burning of external genitalis during micturition was noted. Generalised headache and lethargy occurred rarely. Skin effects are discussed under the skin section. No controls were used.

Rengstorff (1969) reviewed the experience of the US army installation at Edgewood Arsenal, Maryland, regarding the ocular effects of CS.[45] It was noted that the Edgewood Arsenal had studied many aspects of CS, including its effects on volunteers. A study by Punte et al (1963) involved groups of men exposed to various concentrations of CS aerosols in a wind tunnel. It was noted that eyes were affected by instantaneous and severe conjunctivitis, accompanied by burning and pain. The burning and pain persisted for two to five minutes, conjunctivitis remained intense for up to 30 minutes, erythema of the eyelids persisted for about one hour. Lacrimation persisted for about 15 minutes and blepharospasm occasionally occurred. They found that no subject had more than transient effects. Another study by the author himself (Rengstorff 1969), also exposed men to CS aerosols in a wind tunnel and confirmed these observations. In addition, visual acuity was observed. During exposure to low concentrations for 10 minutes, all subjects were able to open their eyes for a few seconds, although with considerable difficulty. Their visual acuity was decreased slightly. During exposure to concentrations higher than 5 mg per cubic metre for 10 minutes, eye irritation was intense with an inability to keep eyes open. Visual acuity was normal several minutes after exposure for all subjects.

Beswick et al (1972) conducted a trial of 35 healthy male volunteers exposed to a cloud of CS in a chamber for 60 minutes.[46] The cloud of CS was generated from either ignition of 1-g pellets of CS or by pyrotechnic devices similar to cartridges. The concentration of CS aerosol remained constant in two of the trials (approximately 0.78 mg per cubic metre). While in the remaining eight trials the concentration of CS aerosol doubled, trebled or increased by four (initially 0.42 to 0.63 mg per cubic metre; finally 1.70 to 2.30 mg per cubic metre). Subjects were examined immediately before and after the exposure and most were seen 24 hours later. Results were presented for 34 subjects as one left the chamber after 8 minutes due to adverse effects. Effects complained of or observed and the number of subjects so affected follow. Eyes: stinging (32), watering (32), blepharospasm (most). Nose: stinging (18), rhinnorrhoea (28), peppery feeling in nose (17), blocked nose (11). Mouth: irritation (15), salivation (34). Throat: irritation (23), dry (8). Respiratory tract: chest burning (8), tight chest (11), dyspnoea (9), cough (18). Gastrointestinal: nausea (11), vomiting (2). Vomiting was isolated and appeared to follow swallowing of large quantities of saliva. Skin: facial stinging (32). Headache, appeared to be related to irritation of frontal sinuses (6, occurred post-exposure in 3 of 6). Symptoms disappeared spontaneously within 10 minutes of moving into clean air in most subjects. 10 subjects reported more persistent symptoms, which did not last for more than 30 minutes, although headache persisted for "somewhat longer" in three subjects. The authors considered there was evidence of tolerance [only 1 of 8 subjects tolerated a fourfold increase in CS compared to 7 of 8 subjects when the fourfold increase in its concentration occurred over a period of one hour]. 16 subjects had their blood haematology and blood biochemistry measured before, immediately after and 24 hours after CS exposure. There was a significant increase in white blood cell count and lymphocyte count at 24 hours while significant increases in neutrophil count, monocyte count and packed cell volume that were evident immediately after exposure, were not apparent at 24 hours [compared to pre-exposure values]. There

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[45] Rengstorff R (1969). Tear gas and riot control agents: a review of eye effects. Optometric Weekly Sep 11: 25-28. ID 27083.

[46] Beswick F, Holland P, Kemp K (1972). Acute effects of exposure to orthochlorobenzylidene malononitrile (CS) and the development of tolerance. Brit J Industr Med 29: 298-306. ID 26872.

was a significant increase in SGPT, total protein, globulin and bicarbonate immediately after CS exposure that had returned to pre-exposure levels at 24 hours for the first two variables. There was a significant decrease in serum sodium, chloride and potassium immediately after CS exposure that had returned to pre-exposure levels for potassium at 24 hours. None of the increases in blood parameters mentioned led to a level that would be considered abnormal. An ECG was performed pre and post-CS exposure in 10 subjects. The pattern of the ECG remained unchanged, however a significant fall in heart rate was observed (pre-CS 80, post-CS 67). Blood pressure was measured before and during CS exposure in 27 subjects. There was a significant steep rise immediately at CS exposure in both systolic [from 122.7 to 142.0 mmHg, p < 0.001] and diastolic blood pressure [73.1 to 84.4 mmHg, p < 0.001] compared to pre-CS levels. However, after 20 minutes exposure to CS, blood pressure levels had returned to pre-CS levels [systolic BP 123.7; diastolic BP 74.5 mmHg]. Chest x-rays showed no differences after CS exposure compared to pre-CS exposure in the 34 subjects examined. Respiratory function tests [peak flow, tidal volume, vital capacity] were measured before, immediately after and 24 hours after CS exposure in 26 subjects. There appeared to be no effect on these parameters from CS exposure. The authors concluded that the changes detected in certain blood parameters, heart rate and blood pressure were physiological and probably due to stress rather than specific to CS. Some of the subjects were seen up to three weeks after exposure (number not specified) with no evidence of after effects. No control group was used.

Cotes et al (1972) conducted a trial on 11 healthy servicemen aged between 18 and 26 years, of the effect of CS aerosol upon lung gas transfer (transfer factor) and alveolar volume.[47] Measurements of transfer factor, transfer coefficient for carbon monoxide and alveolar volume were made by single breath carbon monoxide method with a single breath determination of alveolar volume. CS aerosol was generated by ignition of a CS pyrotechnic device. Exposure to CS aerosol was on the morning of the second day for approximately one hour and the concentration of CS was increased progressively from about 0.6 to 2.0 mg per cubic metre. Pulmonary measurements were made four times a day for the day prior to CS exposure, the day of CS exposure and the day following CS exposure. No changes were observed in the alveolar volume or its components, vital capacity and residual volume, during the study. Exposure to CS aerosol was followed immediately by a significant increase in transfer factor (42.1 to 44.1) and subsequently by a transient decrease to below the initial value (38.4 three hours post-CS; 41.1 five hours post-CS). The mean value in transfer factor was still significantly lower on the day after CS exposure compared to the day prior to CS exposure (40.9 versus 42.6, p < 0.05). These changes were considered of small magnitude and insufficient to exert any material effect upon gas exchange. The small changes in transfer factor were considered to reflect variations in pulmonary capillary blood volume as a result of changes in cardiac output. The latter was felt to be an indirect result of the procedure, rather than specific to CS. Support for this view came from a further study in which the heart rate was measured on nine subjects, the day before, after exposure to 45 minutes of CS aerosol and the day after exposure. The heart rate was increased after exposure to CS (82 per minute) compared to the preceding day (75.1 per minute) and subsequent day (73.6 per minute). There was no control group in either study.

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[47] Cotes J, Dabbs J, Evans M, et al (1972). Effect of CS aerosol upon lung gas transfer and alveolar volume in healthy men. Quarterly Journal of Experimental Physiology 57: 199-206. ID 26805.

Cole et al (1975) conducted a laboratory study on the effects of CS aerosol on exercise ventilation and cardiac frequency in 17 healthy male volunteers.[48] Subjects were exposed to CS aerosol, at a dose of 0.4 to 4.4 mg per cubic metre. Measurements (including a progressive submaximal exercise test) were made on three control days and during exposure to CS. The conditions were similar except that during CS exposure the ambient temperature increased compared to control days (24 degrees C vs. 20 degrees C). Cardiac frequency was increased by exposure to CS by on average 6 per minute ($p < 0.05$), from 101.3 to 107.3 per minute. Exercise ventilation was decreased during CS exposure by a mean of 1.5 l per minute ($p < 0.01$), from 25.1 to 23.6 l per minute. The respiratory frequency was increased slightly by CS exposure. The authors considered that in the dosage tested, the cardiorespiratory response to CS was small in relation to the associated intense discomfort. The increase in cardiac frequency during CS exposure was considered to be the result of the rise in ambient temperature. The reduction in ventilation volume may be due to the CS aerosol stimulating receptors in the respiratory tract.

Foster and Weston (1986) assessed pain produced by various chemical irritants, including CS, when applied to the skin of a small number of human volunteers (n = 5).[49] Volunteers were colleagues of the authors. Blisters were induced with cantharidin and CS solution (in ethanol 0.1%) was applied to the base of the blister and the subject, blinded to the identity of the drug, scored any pain produced. CS was observed to elicit pain (at 100 umol/L pain was scored 8 out of a maximum of 10) but was less potent than another chemical irritant CR. Three volunteers were also given four consecutive applications of CS (100 umol/L) or a control ethanolic solution. They were then re-challenged with the same concentration of CS. No pain was elicited by CS after consecutive applications of CS. In contrast, CS elicited a pain score of 8, after consecutive applications of the control ethanol solution. Hence the authors considered that self-desensitisation had occurred with CS. The blister base test involved a subjective assessment of pain.

Wheeler et al (1998) presented a series of 597 patient inquiries to the National Poisons Information Service, London, during 1997, concerning crowd control agents [CS, mace (chloracetothenon) and pepper spray].[50] Analysis of these inquiries found that 454 (76%) were within six hours of exposure and 143 (24%) were made after six hours. 11% of the latter were made more than 36 hours after exposure. There were significant increases in dermal and gastrointestinal symptoms reported at least six hours after exposure compared to reports within six hours of exposure. The authors considered that their findings indicated delayed adverse effects from CS spray. Clinical effects reported for the two time periods were presented in the following table:

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[48] Cole T, Cotes J, Johnson G, et al (1975). Comparison of effects of ammonia and CS aerosol upon exercise ventilation and cardiac frequency in healthy men. Proceedings of the Physiological Society July: 28-29. ID 27829

[49] Foster R, Weston K (1986). Chemical irritant algesia assessed using the human blister base. Pain 25: 269-278. ID 27443.

[50] Wheeler H, MacLehose R, Euripidou E, et al (1998). Surveillance into crowd control agents. Lancet 352: 991-2. ID 23894.

Number (%) of patients with various clinical effects reported within 6 hours of exposure	Number (%) of patients with various clinical effects reported > 6 hours after exposure	P value
Ocular (irritation, lacrimation) 191 (32)	Ocular (irritation, corneal abrasion) 215 (36)	0.2
Dermal (rash, irritation, erythema, dermatitis) 54 (9)	Dermal (blisters, bullae, eczema, oedema) 203 (34)	< 0.0001
Respiratory (coughing, shortness of breath) 30 (5)	Respiratory (coughing, shortness of breath) 24 (4)	0.37
Neurological (headache, drowsy) 60 (10)	Neurological (headache, drowsy) 42 (7)	0.02
Cardiac (tachycardia, hypotension) 24 (4)	Cardiac (chest pain) 36 (6)	0.26
Gastrointestinal (buccal irritation, vomiting) 42 (7)	Gastrointestinal (buccal irritation, vomiting) 66 (11)	< 0.0001
None 48 (8)	None 6 (1)	
Clinical effects not stated by inquirer 119 (20)	Clinical effects not stated by inquirer 3 (0.5)	
Other 30 (5)	Other 3 (0.5)	

Breakell and Bodiwala (1998) reported on a case series of 23 young people exposed to CS aerosol in an enclosed space, a nightclub, and required attendance at the local emergency department in Leicester, UK.[51] Subjects were exposed to CS for 10 to 15 minutes and presented for treatment approximately 20 minutes after exposure. 12 subjects complained of minor symptoms and discharged themselves before being seen by a doctor. 11 subjects complained of severe eye irritation and respiratory problems (difficulty breathing, chest tightness, and choking sensation). Six patients required eye irrigation. Seven patients required oxygen for breathing difficulties.

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[51] Breakell A, Bodiwala G (1998). CS gas exposure in a crowded night club: the consequences for an accident and emergency department. J Accid Emerg Med 15: 5657. ID 26792.

Effects on the Eyes

Human Volunteer Studies

Rengstorff (1969) performed a series of studies on the ocular effects of CS in male volunteers.[52] The first study involved 10 volunteers individually exposed to particles of CS2 powder (CS treated with Cab-o-sil 5 and hexamethyldisilaxane) in a wind tunnel, the concentration varied from 0.1 to 1.7 mg per cubic metre and the duration of exposure varied from 20 seconds to 10 minutes. The second study involved 34 volunteers exposed in groups of two to four to CS aerosol, thermally disseminated from a methylene dichloride solution, in a steel chamber. The CS concentration varied from 0.4 to 1.0 mg per cubic metre and the duration of exposure varied from 30 seconds to 10 minutes. Far and near visual acuity were measured by an Orthorater before and within a few minutes after exposure to CS. Changes in both far and near visual acuity ranged from +2 to -2 in both studies. The mean change in far visual acuity was -0.4 and in near visual acuity it was +0.4. These changes were considered small. No apparent relationship between changes in visual acuity and CS concentration was evident. A third study involved 22 volunteers with normal baseline visual acuity (20/20) exposed to CS as in the second study. The CS concentration varied from 0.5 to 6.7 mg per cubic metre and the duration of exposure was 10 minutes. Far visual acuity was measured by a Snellen projector before, during and a few minutes after exposure to CS. The visual acuity during exposure to CS ranged from 20/30 to 20/20. All subjects had normal visual acuity (20/20) minutes after the exposure ceased. The authors also observed that subjects profusely lacrimated and had marked conjunctival injection after CS exposure ceased. During exposure to low concentrations, all subjects were able, with considerable effort, to open their eyes for a few seconds. Their visual acuity decreased slightly. During exposure to concentrations higher than 5.0 mg per cubic metre, eye irritation was intense and most subjects could not keep their eyes open for even a few seconds. No control group was used.

Rengstorff and Mershon (1971) performed a laboratory study of the ocular effects of CS in trioctyl phosphate in 20 US Army male volunteers.[53] Subjects were aged from 19 to 27 years and had no ocular abnormality and normal visual acuity on eye examination prior to the experiment. The right eye of each subject was exposed to the test substance while the left eye served as control. Ocular examinations were conducted from 3 to 15 minutes after exposure, at 24 hours (slitlamp) and at either 30 or 36 days later (slitlamp). Two subjects were tested with only a drop of trioctyl phosphate (TOF, a solvent). They felt no irritation and visual acuity was normal within 15 seconds. 10 subjects were tested with a drop of 0.05% to 1.0% CS in TOF. 8 subjects were tested with the spray of CS in TOF (from 0.1% to 1.0%). All subjects exposed to CS-TOF experienced ocular pain, described as an intense burning in the eyes. This improved after a few minutes and no pain was present after 10 minutes. No pain was reported on any subsequent examination. Acute conjunctival injection and tearing occurred instantaneously in all subjects. Tearing subsided after 5 minutes and conjunctivae appeared normal after about one hour. No corneal abnormality was

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[52] Rengstorff R (1969). The effects of the riot control agent CS on visual acuity. Military Medicine March: 219-221. ID 27105.
[53] Rengstorff R, Mershon M (1971). CS in trioctyl phosphate: effects on human eyes. Mil Medicine 136: 152-3. ID 27337.

detected immediately after exposure and at 24 hours or 36 days (drop) or 30 days (spray). Visual acuity was normal within 10 minutes of exposure in all subjects.

Rengstorff and Mershon (1971) performed a laboratory study of the ocular effects of 0.1% and 0.25% CS in water with 0.5% polysorbate 20 in 16 US Army male volunteers.[54] Subjects were aged from 19 to 27 years and had no ocular abnormality and normal visual acuity on eye examination prior to the experiment. The right eye of each subject was exposed to the test substance while the left eye served as control. Ocular examinations were conducted from 3 to 15 minutes after exposure (slitlamp), at 24 hours (slitlamp) and at either 52 or 8 days later (slitlamp). 10 subjects were tested with a drop of 0.1% or 0.25% CS. 6 subjects were tested with a spray of either 0.1% or 0.25% CS. All subjects exposed to CS-water experienced ocular pain, described as an intense burning in the eyes. This improved after a few minutes and no pain was present after 10 minutes. No pain was reported on any subsequent examination. Marked conjunctival injection and tearing occurred instantaneously in all subjects but conjunctivae appeared normal after about one hour. Superficial corneal staining (4 mm by 0.5 mm) was present in one subject exposed to the CS-water spray immediately after exposure but was no longer evident at the 24-hour examination or later. No corneal abnormality was detected in other subjects immediately after exposure and at 24 hours or 52 days (drop) or 8 days (spray). Visual acuity was normal within 3 minutes of spray exposure in all subjects. There did not appear to be significant differences in visual effects from the two concentrations in either the eye drop or spray test.

Ballantyne and Swanston (1973) conducted laboratory tests on the irritant potential of solutions of ortho-chlorobenzylidene malononitrile (CS) in normal saline on the eye of 10 humans, 10 rabbits and 10 guinea pigs.[55] Young adult male volunteers free from allergies and with no ocular history were used. The median threshold concentration that produced blepharospasm in the rabbit was 0.000059 M, in the guinea pig it was 0.000022 M, and in the human it was 0.0000032 M. Hence the human eye was about seven times more sensitive than the eye of the guinea pig and about 18 times more sensitive than the eye of the rabbit. The threshold concentration that produced corneal sensation (based on subject self-response) in man was 0.00000073 M. A dose-response relationship was demonstrated. Based on other experiments, the authors noted that the human eye was considerably more sensitive to CS in aerosol form than in solution. The authors also noted that there was a 6650 fold difference between the concentration of CS likely to cause just detectable transient damage to the cornea and the highest concentration used in these irritancy threshold studies.

Case Reports / Series

There were several articles in the literature that reported permanent or ongoing serious ocular injuries from tear-gas weapons (both explosive type and spray type) fired at close distance to the subject's face.[56][57][58][59] Other articles expressed concern about

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[54] Rengstorff R, Mershon M (1971). CS in water: II effects on human eyes. Mil Medicine 136: 149-151. ID 27415.

[55] Ballantyne B, Swanston D (1973). The irritant potential of dilute solutions of ortho-chlorobenzylidene malononitrile (CS) on the eye and tongue. Acta Pharmacol Et Toxicol 32: 266-77. ID 27453

[56] Hoffmann D (1967). Eye burns caused by tear gas. Brit J Ophthal 51: 265-268. ID 26783

this possibility.[60][61] The ocular injury resulted from the force of the blast, fragments of the container used to hold the chemical as well as the chemical agent. None of these articles specifically implicated CS, stating that chloroacetophenone (CN) was the most common chemical irritant involved.

Several ophthalmologists and eye units reported their experience with ocular injury from CS exposure in the UK.[62][63][64] Conjunctival injection and occasionally corneal punctate epithelial erosions were mentioned as well as a report of acquired dry eye states in three police officers following a "demonstration" of CS aerosols.[65] But all authors reported an absence of long-term ocular sequelae. A latter report by a UK ophthalmologist (2000) noted that experimental studies had shown that high concentrations of CS, especially in solution, when applied to the eye, caused ocular damage [Ballantyne et al 1974] and a report of cases with significant ophthalmological sequelae [Petersen et al 1989 - non-English].[66] He also noted that he had seen several patients and police constables after the use of CS and these were awaiting judicial consideration for the award of damages.

Ferslew et al (1986) described an incident where a jar of yellowish-white powder was found by police officers in a Tennessee mall.[67] Attending police officers developed lacrimation, burning of the skin and eyes, rhinorrhoea, coughing and dyspnoea. Treatment was required at the local eye hospital for severe eye irritation. Spectral data (ultraviolet, fluorescence, proton nuclear magnetic resonance, infrared) and a gas-liquid chromatographic / mass spectrometric method identified the powder as CS. No details were given about any ongoing ocular complications.

Bhattacharya and Hayward (1993) reported the case of a previously healthy 19-year old male sprayed in the face with CS, and who also suffered from stab wounds.[68] He underwent abdominal surgery for a stab wound at a Middlesex hospital. Postoperatively, the patient developed conjunctivitis that cleared within two days.

Parneix-Spake et al (1993) presented a case series of 11 patients hospitalised in a Paris university hospital, over a three-year period with bullous dermatitis, after having

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[57] Levine R, Stahl C (1968). Eye injury caused by tear-gas weapons. Am J Ophthalmology 65: 497-508. ID 26867

[58] Leopold I, Lieberman T (1971). Chemical injuries of the cornea. Federation Proceedings 30: 92-95. ID 27511.

[59] Oksala A, Salminen L (1975). Eye injuries caused by tear-gas hand weapons. Acta Ophthalmologica 53: 908-913. ID 26879

[60] Gray P (1995). Treating CS gas injuries to the eye: Exposure at close range is particularly dangerous. Letter to editor. BMJ 311: 871. ID 26810

[61] Gray P (1997). CS gas is not a chemical means of restraining a person. Letter to editor. BMJ 314: 1353 ID 26787

[62] Yih J-P (1995). CS gas injury to the eye. BMJ 311: 276 ID 26786.

[63] Gray P (1997). Letter to the editor. Eye 11: 949-950. ID 26784.

[64] Willoughby C, Ilango B, Hughes A (1998). Letter to the editor. Eye 12: 164. ID 26785.

[65] Gray P (1997). Letter to the editor. Eye 11: 949-950. ID 26784.

[66] Gray P (2000). Re: Is CS spray dangerous? Formulation affects toxicity. BMJ 321: 46. ID 27419

[67] Ferslew K, Orcutt R, Hagardorn A (1986). Spectral differentiation and gas chromatographic / mass spectrometric analysis of the lacrimators 2-chloroacetophenone and o-chlorobenzylidene malononitrile. Journal of Forensic Sciences 31: 658-665. ID 27461

[68] Bhattacharya S, Hayward A (1993). CS gas - implications for the anaesthetist. Anaesthesia 48: 896-7. ID 26791.

been sprayed with CS [more details under "skin"].[69] Three cases had associated keratitis (out of nine that had an ophthalmologic examination).

Anderson et al (1996) reported on a case series of 184 people exposed to CS "gas" at a Vietnamese detention centre in Hong Kong and who complained of symptoms consistent with the effects of CS within 21 days of the incident.[70] 1500 people were exposed to CS in total. Large amounts of CS were used in a confined space and detainees were not transferred out of the contaminated area for eight hours. Significantly symptomatic subjects were seen by a British Red Cross clinic physician. Some of those with minor symptoms were not assessed. The age of the patients ranged from 3 months to 57 years (mean 24 years). The number of clinic visits varied from one to six per patient, but only two patients required more than three visits (excluding those with burn dressings). The time to first presentation at the clinic ranged from < 1 day to 19 days (mean 5 days). Due to the time delay of 6 to 8 hours between exposure and access to the clinic, only 2% of patients complained of ocular pain, lacrimation or blurred vision. Four patients had mild conjunctivitis. There were no cases of keratitis.

Kiel (1997) described six patients brought to the Southhampton Eye Unit after a substance was sprayed into the doorway of a public house (thought to be CS).[71] Two were directly hit in the face while the others were indirectly affected. Ocular examination 30 minutes after exposure revealed only slight conjunctival injection. The following day all patients were asymptomatic. No ongoing ocular sequelae were mentioned.

Breakell and Bodiwala (1998) reported on a case series of 23 young people exposed to CS aerosol in an enclosed space, a nightclub, and required attendance at the local emergency department in Leicester, UK.[72] 11 subjects complained of severe eye irritation and respiratory problems, and six of these required eye irrigation. There was no mention of any ongoing ocular sequelae.

The case report by Hill et al (2000) [more details under "skin"] of a 30-year old Hispanic male prison inmate heavily "sprayed" with CS and subsequently treated at a Brooklyn hospital.[73] Eight days after exposure, the patient was hospitalised and physical findings included injected and mildly icteric conjunctivae.

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[69] Parneix-Spake A, Theisen A, Roujeau J, et al (1993). Severe cutaneous reactions to self-defense sprays. Arch Dermatol 129: 913.

[70] Anderson P, Lau G, Taylor W, et al (1996). Acute effects of the potent lacrimator o-chlorobenzylidene malononitrile (CS) tear gas. Human and Experimental Toxicology 15: 461-5. ID 26803.

[71] Kiel A (1997). Ocular exposure to CS gas: the importance of correct early management. Eye 11: 759-60. ID 27399.

[72] Breakell A, Bodiwala G (1998). CS gas exposure in a crowded night club: the consequences for an accident and emergency department. J Accid Emerg Med 15: 5657. ID 26792.

[73] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.

Animal Studies

Rengstorff and Mershon (1971) also discussed previous animal studies on the ocular effects of CS in water.[74] Owens and colleagues (Edgewood Arsenal Technical Report 1969) demonstrated that 1.0% CS-water slurry caused no significant damage to rabbit or monkey eyes. Rengstorff and colleagues (Edgewood Arsenal Technical Report 1969) showed negligible effects, when over 500 ml of 0.5% CS in water was sprayed on rabbit eyes.

Ballantyne et al (1974) conducted a laboratory study on the ocular effects in rabbits of CS in solution (0.5% to 10% in polyethylene glycol 300), CS as a solid (0.5 to 5mg), and CS as a pyrotechnically generated smoke (15 minute exposure to 6 g per cubic metre).[75] Experiments were carried out using 168 adult albino rabbits; each concentration of CS was tested in 10 rabbits. CS in solution and in solid was introduced into the conjunctival sac of the right eye and the left eye used as an untreated control. The smoke was generated from the detonation of a grenade that contained a mixture of 25% CS, 30% potassium chlorate, 30% lactose and 15% kaolin. Rabbits were examined for up to one week for experiments involving CS as a solid and as a smoke and for up to 45 days for CS as a solution. CS caused lacrimation, blepharitis, and conjunctival irritation by all methods of contamination, the severity and duration of which increased with the amount of material applied. Effects were most severe with CS in solution, less with CS solid and least marked with CS smokes. Lacrimation, blepharitis, and conjunctival irritation varied from mild degree lasting 24 hours with 0.5% CS solution to moderately severe and of two weeks duration with 10% CS solution. Mild and transient keratitis and iritis occurred with 1% CS solution, being more severe and prolonged with the higher concentrations. All rabbits treated with 10% CS solution developed an iritis, which varied from mild to moderate and of 2 to 7 days' duration. Keratitis was still present 57 days after exposure to 5% CS solution in one rabbit and 45 days after exposure to 10% CS solution in another rabbit. Vascularisation of the cornea was observed in five rabbits treated with either 5% or 10% CS in solution and took up to 7 days to resolve. Histological examination of eyes from animals sacrificed whilst a keratitis was still present, demonstrated patchy denudation of corneal epithelium, a thickened substantia propria and neutrophil infiltration of the cornea. Eyes that appeared macroscopically normal, had no histological abnormalities. Keratitis was not seen after exposure to CS smokes and superficial corneal damage of short duration (24 hours) occurred only in a few animals treated with 5mg solid CS. A concentration-dependent significant increase in intra-ocular tension, of less than one-hour duration, occurred with CS in solution. There was a 52% increase in intra-ocular pressure 10 minutes after exposure to 5% CS solution but this had returned to normal at one hour. The authors noted that whilst most of the inflammatory effects were reversible, keratitis that occurred with 5% CS solution, although mild, was persistent. They also noted the role of the solvent in CS solutions, since it might affect both the nature and duration of any effects produced by the active agent. They commented that Gaskins et al (1972) found that 10% CS in 1,1,1-trichlorethane did not induce corneal damage.

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[74] Rengstorff R, Mershon M (1971). CS in water: II effects on human eyes. Mil Medicine 136: 149-151. ID 27415.

[75] Ballantyne B, Gazzard M, Swanston D, et al (1974). The ophthalmic toxicology of o-chlorobenzylidene malononitrile (CS). Arch Toxicol 32: 149-168. ID 27840

Ballantyne (1979) conducted a laboratory study on the ocular effects of CS produced from an aerosol generator discharged at 6 inches and two feet from the eyes of 12 rabbits.[76] 10% CS in dichloromethane, pressurised with dichlorodifluoromethane was used. The exposure was for one second (which delivered approximately 10 mg of CS). Animals were observed for 21 days and then histological examination of the eyes was conducted. The effect at six inches on six rabbits: lacrimation subsided over 3 days; conjunctival injection subsided over 8 days; oedema subsided over 7 days; blepharitis persisted for about two weeks; contracture of the eyelid margins resolved during the second week; and transient just detectable iritis occurred in two rabbits during the first week. Diffuse keratitis at 24 hours in three rabbits was observed. This resolved by 3 days in one rabbit, one week in a second rabbit, but was still present with corneal ulceration at three weeks in a third rabbit and confirmed by histology. The effect at two feet on six rabbits were mild lacrimation of less than one hour duration in two rabbits and mild conjunctival injection in two rabbits (resolved by 24 hours). The author considered that the ocular effects were due to the combined action of CS and the solvent dichloromethane. The author noted that a previous experiment of his that involved splash contamination of the eye with 10% CS, in the comparatively inert solvent polyethylene glycol 300, had also caused a marked and persistent keratitis. But smokes containing up to 6 g CS per cubic metre of air had not damaged the eye (Ballantyne et al 1974).

Ballantyne (1985) studied the acute toxicity of CS in animal experiments.[77] Six adult female albino rabbits had 10 mg amounts of CS placed in the inferior conjunctival sac of the right eye. Eyes were inspected for the following two weeks. There was mild to moderate lacrimation of about three days duration, mild to moderate blepharitis and conjunctival injection lasting six to seven days, mild chemosis for three days, and mild iritis and keratitis that appeared at 24 hours and persisted for three to six days. Histological examination of eyes removed at two weeks post-CS exposure were normal. Eyelids had normal epidermis but there was hypertrophy and proliferation of meibomian glands, goblet cell proliferation in the palpebral epithelium and residual inflammatory changes in the dermis.

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[76] Ballantyne B (1979). Evaluation of ophthalmic hazards from an aerosol generator of 2-chlorobenzylidene malononitrile (CS). Military Medicine 144: 691-4. ID 27445
[77] Ballantyne B (1985). Acute toxicity and primary irritancy of 2-amino-3,5-dicyano-4-o-chlorophenyl-6-ethoxypyridine. Drug and Chemical Toxicology 8: 171-182. ID 27785

Effects on the Respiratory Tract

Human Volunteer Studies

Punte et al (1963), from the US Army Chemical Research and Development Laboratory, reviewed the results of exposure of human volunteers to CS.[78] Seven subjects were exposed ten times to CS [1 to 13 mg per cubic metre] during a period of two weeks. No abnormalities were shown on chest x-rays taken before and two months after CS exposure. No significant change was observed in airway resistance measured by the Asthometer, before, after the fourth exposure, after the tenth exposure and 24 hours after the tenth exposure. No controls were used.

Case Reports / Series

Concern about CS was raised after CS was used in Derry, Northern Ireland in 1969.[79] McClean (1969), a local medical officer, treated upwards of 200 cases of CS exposure during the Derry disturbances.[80] Approximately 1000 cartridges and 14 hand-grenades of CS was fired into an area of Derry over a period of 48 hours with many residents exposed to a varying but constantly irritating atmospheric concentration of CS. The local doctor described the case of a 22-year old male exposed to CS during this period. He had a history of very minor attacks suggestive of an asthmatic complaint in childhood and an episode of asthmatic bronchitis the previous year. His spirometry (FEV1/FVC) the previous year was 72%. He attended the doctor 2 weeks after CS exposure with symptoms of chest tightness since that exposure. Examination revealed bronchospasm. The FEV1/FVC ratio was reduced to 58%. Treatment included antibiotics and anti-asthma medication. About three weeks after CS exposure, the patient had symptomatically improved but clinical examination still demonstrated bronchospasm and spirometry remained reduced [FEV1/FVC 63%]. No further follow-up had occurred at the time of the article.

Park et al (1972) reported the case of a previously healthy four month old male infant who developed pneumonitis following prolonged exposure to CS.[81] The infant had been exposed to CS "gas" for two to three hours inside a house where police had fired CS tear gas canisters. The infant was seen at a San Francisco hospital. Initial symptoms were upper respiratory. The chest x-ray on admission was clear. On the second hospital day, cyanosis, severe respiratory distress, wheezes and rales in the lung fields were observed. On the seventh hospital day, a chest x-ray demonstrated right upper lung field infiltration and the chest-x-ray was not clear until the 17th day of the illness. A persistently elevated white blood cell count with a predominance of lymphocytes on peripheral blood smear was also noted. The child was hospitalised for 28 days. Treatment included oxygen, positive pressure breathing, and antibiotics. There was no comment about any ongoing respiratory sequelae.

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[78] Punte C, Owens E, Gutentag P (1963). Exposures to ortho-chlorobenzylidene malononitrile. Controlled human exposures. Archives of Environmental Health 6: 72-80. ID 26680
[79] Anonymous (1969). Riot-control agents. BMJ 3: 546. ID 27406
[80] McClean R (1969). Riot-control agents: personal experience. BMJ 3: 652-3. ID 27405
[81] Park S, Giammona S (1972). Toxic effects of tear gas on an infant following prolonged exposure. Amer J Dis Child 123: 245-6. ID 26869.

Chapman and White (1978) presented the case of a 33-year old white male prison inmate who died following the use of tear gases at a Oklahoma prison.[82] During the use of the tear gases, inmates were confined to their cells, ventilating fans were turned off, and windows and doors were closed. The duration of the exposure was approximately 110 minutes. It consisted of a minimum of six heat-type grenades of the tear gas chloroacetophenone (CN), 14 37-mm 100-g projectiles of CN and in excess of 0.4 litre of 8% CS "gas" in two four- to five-minute bursts. Additional smaller amounts of these tear gases were discharged the following day. The person was found dead under his bed approximately 46 hours after the initial exposure to the tear gases. Prior to this, fellow inmates had noticed that the case had red eyes and had vomited material they considered "bloody". A post-mortem examination, which incorporated pathology, found that the cause of death was acute necrotising laryngotracheobronchitis, chemical. Analyses for CN in autopsy material were negative but this was not unexpected due to the period of survival after exposure. Scattered areas of bronchopneumonia, oedema and minimal intra-alveolar haemorrhage were also observed histologically. The authors considered that death was most likely the result of exposure to CN as there have been previous reports of death with similar findings from exposure to CN. The role of CS in this death was unclear; it may have exacerbated the effects of CN or played no role at all.

Pipkin (1990) presented a case series of ten soldiers diagnosed with influenzae A at the UK Commando Training Centre Royal Marines, over a one month period, during autumn 1988.[83] Patients were admitted with significant flu-like symptoms and serology demonstrated a rise in antibody titre to influenzae A virus in nine subjects. Five of these patients were admitted the day after "gas drills" and had experienced brief exposure to CS "gas" with the consequent typical respiratory tract irritation. One of the patients experienced non-productive cough and breathing difficulties on exercise for about the following two months. None experienced significant long-term sequelae. Four other patients had presented prior to and one patient after the CS exposed group with influenzae A. The author raised the possibility of CS exposure worsening the severity of influenzae.

Hu and Christiani (1992) reported the case of a previously healthy 21-year old woman who developed reactive airways dysfunction syndrome after accidental exposure to CS.[84] She had no personal or family history of asthma or atopy. Exposure occurred in a crowded nightclub when a canister containing CS discharged at a distance of two to three metres and exposure lasted for 5 to 10 minutes. Symptoms of burning of the eyes, face, throat, nasal passages, paroxysmal coughing, and tightness of chest developed immediately. Physical examination and chest x-ray at hospital was normal. Two weeks after CS exposure, coughing and wheezing required hospitalisation and treatment with intravenous steroids, antibiotics, theophylline and beta agonists. Four weeks after CS exposure, spirometry demonstrated a reduced FEV1 (62% predicted) and reduced forced vital capacity (78%). Symptoms continued during two years of

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[82] Chapman A, White C (1978). Death resulting from lacrimatory agents. J Forensic Sci 23: 527-30. ID 27095.

[83] Pipkin C (1990). Does exposure to CS gas potentiate the severity of influenza? Journal of the Royal Naval Medical Service 76: 188-9. ID 27831

[84] Hu H, Christiani D (1992). Reactive airways dysfunction after exposure to teargas. Lancet 339: 1535. ID 26788.

follow-up and the patient is on daily medication of inhaled beta-agonists and steroids, with intermittent oral steroids.

Bhattacharya and Hayward (1993) reported the case of a previously healthy 19-year old male sprayed in the face with CS "gas", and who also suffered from stab wounds.[85] Postoperatively, the patient developed a small pleural effusion and left basal pneumonic patch. This appeared to clear, although the time taken was not stated. The patient had another risk factor for the infective process - the anaesthetic for the surgery.

Roth and Franzblau (1996) presented the case of a previously healthy 51-year old male prison guard diagnosed with reactive airways dysfunction syndrome (RADS) after exposure to a riot-control agent, Deep Freeze [1% orthochlorobenzalmalonitrile, 1% oleo resin capsicum in a solvent blend containing an ultraviolet dye].[86] The subject experienced immediate symptoms of mucous membrane irritation, cough and chest tightness. Several months after this exposure the subject had persistent symptoms and signs consistent with RADS; decreased exercise tolerance, fatigue, chronic cough, wheezing, and pulmonary function tests consistent with both reversible and fixed obstructive pulmonary disease. Approximately three to four years after exposure, symptoms had persisted and required medication. However, exposure to the agent was indirect; a mattress previously sprayed with the agent was turned over and the subject was exposed for at least 30 seconds.

Anderson et al (1996) reported on a case series of 184 people exposed to CS "gas" at a Vietnamese detention centre in Hong Kong and who complained of symptoms consistent with the effects of CS within 21 days of the incident.[87] The time to first presentation to a clinic physician ranged from < 1 day to 19 days (mean 5 days). At the first visit, 38% of patients complained of cough (maximum duration 22 days), and 21% complained of shortness of breath (maximum duration 33 days). 15-20% of patients complained of chest pain at visit one but only about 1% by visit three (22 to 27 days). 10-15% of patients complained of fever at visit one but this was confirmed clinically in about 4%. Complaints of fever were present in only 1-2% of patients at visit three. 15 patients claimed to have had haemoptysis at visit one but this was confirmed by a sputum sample in only one patient and his chest x-ray was normal. Six patients had wheeze and 10 patients had crepitations on clinical examination. Three patients were known asthmatics and two patients had a history of pulmonary tuberculosis. There was no evidence of prolonged dysfunction in these patients apart from a ten-year old asthmatic girl who complained of dyspnoea for 33 days and had low peak expiratory flow readings [but lung function was not seriously affected]. One patient was admitted to hospital with pneumonia shortly after removal from CS exposure but it was unclear whether this episode was a CS-related chemical pneumonitis.

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[85] Bhattacharya S, Hayward A (1993). CS gas - implications for the anaesthetist. Anaesthesia 48: 896-7. ID 26791.
[86] Roth V, Franzblau V (1996). RADS after exposure to a riot-control agent: a case report. JOEM 38: 863-65.
[87] Anderson P, Lau G, Taylor W, et al (1996). Acute effects of the potent lacrimator o-chlorobenzylidene malononitrile (CS) tear gas. Human and Experimental Toxicology 15: 461-5. ID 26803.

Breakell and Bodiwala (1998) reported on a case series of 23 young people exposed to CS aerosol in an enclosed space, a nightclub, and required attendance at the local emergency department in Leicester, UK.[88] 11 subjects complained of severe eye irritation and respiratory problems (difficulty breathing, chest tightness, and choking sensation) and seven of these required oxygen for breathing difficulties. Two of the subjects requiring supplemental oxygen suffered from asthma. Clinically none of the patients developed wheeze but one asthmatic patient required a nebuliser for chest tightness. One previously healthy patient was admitted to hospital for 24 hours with persistent chest tightness and sore throat. The chest tightness had resolved on discharge but the sore throat persisted. Peak flow values were unchanged between admission and discharge in patients with respiratory symptoms. There was no mention of any ongoing respiratory sequelae.

Bayeux-Dunglas et al (1999) presented the case of a 26-year old female teacher with no history of respiratory disease who developed an asthma-like illness after repeated exposure to CS tear gas discharged in her class-room.[89] There appeared to be evidence of moderate bronchial hyperreactivity on methacholine test. The authors considered that the diagnosis was consistent with low level reactive airways dysfunction syndrome. As the paper was written in French, it was unclear whether the onset of symptoms began within 24 hours of the first exposure to CS.

The case report by Hill et al (2000) [more details under "skin"] of a 30-year old Hispanic male prison inmate heavily "sprayed" with CS and subsequently treated at a Brooklyn hospital.[90] A diagnosis of hypersensitivity reaction with bronchoconstriction, pneumonitis, dermatitis and hepatitis was made. The persisting asthma-like disorder was considered to meet the diagnostic criteria for reactive airways dysfunction syndrome

Thomas et al (2002) described nine US marines that developed an acute transient pulmonary syndrome consistent with pulmonary oedema after heavy exposure to a CS cloud in a field-training setting.[91] The nine marines were part of a group of 38 marines that were on an 8-week intensive amphibious reconnaissance-training course. At the time of the CS exposure, all 38 marines had completed six days of arduous training with minimal sleep, restricted food and weather conditions were hot and humid. The 38 marines were exposed to a dense CS cloud thermally generated from canisters dropped at their feet and the exposure lasted up to several minutes while face-masks were put on. The marines then completed a 1.5-mile run. Clinical symptoms were associated with additional strenuous physical exercise with an onset from 36 to 84 hours after exposure to CS. In all nine marines this was a 1-1.5 km pool or open ocean swim. All nine subjects required hospitalisation. They were all previously healthy and eight were non-smokers. All nine patients had cough and dyspnoea, five had haemoptysis (from frank blood to blood-tinged sputum) and four had hypoxia (which

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[88] Breakell A, Bodiwala G (1998). CS gas exposure in a crowded night club: the consequences for an accident and emergency department. J Accid Emerg Med 15: 5657. ID 26792.

[89] Bayeux-Dunglas M-C, Deparis P, Touati M-A, et al (1999). Asthme professionnel chez une enseignante apres inhalation repetee de gaz lacrymogenes. Rev Mal Respir 16: 558-559. ID 27782

[90] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.

[91] Thomas R, Smith P, Rascona D, et al (2002). Acute pulmonary effects from o-chlorobenzylidenemalonitrile "tear gas": a unique exposure outcome unmasked by strenuous exercise after a military training event. Military Medicine 167 (2): 136-139. ID 27679

required intensive care observation). Four had infiltrates on chest x-rays. All symptoms and signs resolved within 72 hours of hospital admission. 8.5 days after CS exposure, all nine subjects demonstrated normal lung function on spirometry before and after exercise challenge and on chest x-rays. An approximate recreation of the conditions was conducted and found that the CS concentration in air ranged from less than quantifiable to about 17 mg CS per cubic metre. The authors noted that approximately 200,000 US marines had been exposed to CS in a tent or building for short periods during gas mask training exercises, since 1996. There have been no reports of similar cases (unpublished data from US Marine Corps Training and Education Command, 2001). Others questioned the relationship to CS exposure, noting the delayed onset of symptoms in association with strenuous swimming and considered that the cases were examples of pulmonary oedema from water immersion.[92]

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[92] McDonald E, Mahon R (2002). Letter to the editor Re: Acute pulmonary effects from o-chlorobenzylidenemalonitrile "tear gas": a unique exposure outcome unmasked by strenuous exercise after a military training event. Military Medicine 167: iii-iv. ID 27683

Effects on the Skin

Reviews

Weigand (1969) [from the Edgewood Arsenal] discussed the cutaneous reaction to the riot control agent CS.[93] Cutaneous reaction to CS exposure was not immediate; stinging that develops within a few minutes was less severe than that affecting the eyes and nose. The author first discussed military situations in which adverse skin reactions have resulted. Most exposures to CS among American troops during the Vietnam War were accidental. Troops with protective masks in contaminated areas were at risk of a skin-damaging exposure because their mask may make them unaware of the presence of CS. High heat and humidity were associated with CS dermatitis. Another high-risk situation was considered to be the "tunnel-rat"; entry into tunnels where many CS grenades have been detonated with resultant high CS concentration. Civil situations were discussed next. The author noted that a CS grenade burns for about 30 seconds, releasing a cloud of thermally generated aerosol particles and this lingers for about 10 to 15 minutes on a calm day. A CS concentration of 2,000 to 5,000 mg per cubic metre is produced at the point of burst and a concentration of 1,000 mg per cubic metre can occur 50 yards downwind in a five mile per hour wind. Relatively brief exposure to these CS concentrations may result in second-degree burns. The author noted that in a recent series of civil disorders, firemen, upon entering burning or burnt-out buildings, developed erythema and oedema of exposed facial and neck skin. The previously disseminated CS was re-aerosolised by the movement of men and spraying of water. In the industrial situation, allergic contact dermatitis in CS-processing workers has been observed [Bowers et al - unpublished data]. The opportunity for repeated exposure was considered to be the main factor in its occurrence. A single exposure resulting in significant inflammation was considered sufficient to sensitise in some cases and very slight later exposures can elicit the eczematous reaction. Experimental studies have demonstrated regional variations in cutaneous reactions to CS. Under simulated tropical conditions, white subjects experienced stinging and erythema on the flexor surface of the forearm during and for 10 to 30 minutes after exposure to a CS concentration of 4,500 or 9,000 mg per cubic metre per minute [ie 300 mg per cubic metre for 15 or 30 minutes] [Hellreich et al - unpublished data]. More prolonged erythema and bullae occurred at a CS concentration of 14,000 mg per cubic metre per minute. However, stinging and erythema on the neck, ears, and forehead occurred at a lower CS concentration (< 1,000) as did bullae on the neck (1,000 to 3,000). Hence exposure to a CS grenade at the point of burst (concentration of 5,000 mg per cubic metre) for 12 seconds (0.2 minutes) was sufficient for the formation of bullae. Erythema of the neck and ears that lasted for 30 to 60 minutes was also observed in humans after exposure to a CS concentration of 25-50 mg per cubic metre per minute, in tropical conditions.

Fisher (1970) reviewed dermatitis due to tear gases.[94] The author stated that all the tear gases producing lacrimation, including CS, in high concentrations were powerful skin irritants and could produce first and second degree burns. CS exposure on moist skin, in particular, could result in third degree burns with ulceration. Irritant dermatitis

[93] Weigand D (1969). Cutaneous reaction to the riot control agent CS. Military Medicine June: 437-440. ID 27102.
[94] Fisher A (1970). Dermatitis due to tear gases (lacrimators). International Journal of Dermatology 9: 91-95. ID 26873.

has been noticed in technicians and others handling lacrimators, especially CS. CS was also a sensitiser and allergic contact dermatitis could result in those exposed by the military or police and in those involved in its manufacture or handling. Allergic contact dermatitis took a typical eczematous form, often accompanied by marked oedema.

Shmunes and Taylor (1973) reviewed some literature that dealt with the cutaneous effects of CS.[95] Irritant effects were discussed first. Gutentag et al (1960) [Chemical Warfare Laboratory Report 2365], observed vesicating reactions on human skin at patch test sites to CS powder and aerosols of 20% CS-methylene dichloride solutions. Hellreich et al (1967) [Edgewood Arsenal Technical Report 4075], exposed human forearms to CS aerosol in chambers that simulated tropical temperatures and humidity. CS concentrations of 4,400 to 9,480 mg per minute per cubic metre produced stinging of forearms five to ten minutes after exposure and erythema one minute after exposure that persisted for 10 to 30 minutes after exposure. CS concentrations of 14,040 and 17,700 mg per minute per cubic metre induced a more severe immediate dermal reaction that subsided within three hours but followed by delayed first- and second-degree burns. Hellreich et al (1969) [Edgewood Arsenal Technical Report 4252] conducted subsequent studies with larger groups and found that in general, 50% of men would develop some degree of erythema when the CS concentration was 3,500 mg per minute per cubic metre in moist and warm air. Other studies conducted at Edgewood Arsenal examined skin reactions to CS in solution rather than in aerosol form [Weigand et al 1969, Edgewood Arsenal Technical Report 4380]. The cutaneous reaction pattern of stinging, early erythema and delayed erythema was similar and enhanced by heat. Weigand and Mershon (1970) [Edgewood Arsenal Training Report 4332] found that black skin compared to white skin required at least double the exposure time to CS2 powder to produce similar erythema. Animal studies in the beagle and albino rabbit by Weigand et al (1970) [Edgewood Arsenal Technical Report 4451] found that the earliest change histologically in patch test sites exposed to CS2 powder for four hours was hydropic degeneration in the basal cell layer. Minimal spongiosis in the prickle cell layer followed within 24 hours. Epidermal necrosis occurred with prolonged exposure to CS. Reports of burns were discussed next. There was a report of 12 men with rain-soaked uniforms on a training mission caught in a cloud of CS1 who developed first- and second-degree burns in exposed areas. In a plant that employed over 100 workers in the manufacture of CS, two workers were hospitalised with second- and third-degree burns. Allergic skin reactions to CS were discussed last. Delayed eczema occurred at a patch test site on the forearm of a human 10 days after a single and first exposure to CS aerosol under simulated tropical climatic conditions [Hellreich et al (1969), Edgewood Arsenal Technical Report 4252]. Skin sensitisation occurred in five of nine subjects topically exposed to a 1% concentration of CS in alcohol [Maibach - oral communication]. Based on clinical observations, five of 11 workers employed at a CS plant, displayed sensitisation after the initial localised dermatitis and reacted more rapidly and over a wider area on reexposure to CS [Bowers et al 1960]. No patch testing was done. Rothberg (1970) induced delayed hypersensitivity in guinea pigs using dilutions of CS topically and intradermally.

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[95] Shmunes E, Taylor J (1973). Industrial contact dermatitis. Arch Dermatol 107: 212-216. ID 26875

Ballantyne (1985) studied the acute toxicity of CS in animal experiments.[96] Following a six-hour dermal contact with 100 mg dry or moist CS in eight rabbits, there was moderate local erythema and mild oedema, which gradually subsided over two to three days. Pathological examination of skin biopsies, taken 18 hours, after removal of the occlusive dressing, revealed spongiosis, and congestion, oedema, and marked neutrophilic infiltration of the dermis. The author considered that CS had produced a moderate local irritant dermatitis.

Sidell (1997) discussed riot control agents, including CS.[97] The author also discussed the human volunteer experiments conducted by Hellreich and colleagues (1967) on the cutaneous effects of CS thermally generated from an M7 grenade. CS aerosol at a concentration of 14,040 and 17,700 mg per minute per cubic metre caused a more severe initial dermal response that required three hours to disappear. After 12 to 24 hours, a delayed reaction of first and second-degree burns was observed. Blistering occurred in four of eight subjects. With treatment, these lesions resolved in 10 to 14 days. Six weeks later, a small amount of post-inflammatory pigmentation remained.

Human Volunteer Studies

Punte et al (1963), from the US Army Chemical Research and Development Laboratory, reviewed the results of exposure of human volunteers to CS.[98] Skin symptoms consisted of burning on exposed skin areas, exacerbated by moisture, and remained for several hours. It recurred upon washing the exposed areas or the hair. Heavy exposures, eg working daily with bulk quantities of CS, produced vesiculation and erythema that resembled second-degree burns. Patch tests (24 hours) were made on subjects using CS or associated compounds. It was found that CS was a potential severe skin irritant. No controls were used. Results were:

Compound	Number of subjects	Results
CS (protected from air)	11	5 - no reaction 2 - slight erythema 4 - erythema, vesicle formation, sloughing
CS (porous gauze covering)	4	4 - erythema, vesicle formation
10% CS - methylene dichloride	3	No reaction
20% CS - methylene dichloride	4	2 - slight erythema
Malononitrile	3	No reaction
o-chlorobenzaldehyde	3	2 - pruritis

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[96] Ballantyne B (1985). Acute toxicity and primary irritancy of 2-amino-3,5-dicyano-4-o-chlorophenyl-6-ethoxypyridine. Drug and Chemical Toxicology 8: 171-182. ID 27785
[97] Sidell F (1997). Chapter 12 Riot Control Agents. In: Textbook of Military Medicine Part 1: Medical Aspects of Chemical and Biological Warfare. Zajtchuk (Ed). Office of the Army Surgeon General, Washington, DC. ID 27592
[98] Punte C, Owens E, Gutentag P (1963). Exposures to ortho-chlorobenzylidene malononitrile. Controlled human exposures. Archives of Environmental Health 6: 72-80. ID 26680

CS mixed with sodium hypochlorite bleach (protected from air)	4	4 - severe reaction with erythema, vesicles, sloughing, induration; 2nd to 3rd degree burn
CS mixed with sodium hypochlorite bleach (porous gauze covering)	4	4 - same as above but more extensive

Maibach and Marzulli (1971), from the University of California Medical School, performed a study of allergic skin sensitisation of riot control agents on 10 adult male volunteers.[99] A modified Draize test was performed which involved application of 5 drops of 1% CS in alcohol placed in a 3-cm diameter ring on the skin. These were uncovered applications. Five out of nine subjects were strongly sensitised to CS. Most of the sensitised subjects also showed skin reactions to 0.1% CS, but not 0.01% CS.

Holland and White (1972) conducted a trial of healthy volunteer servicemen, aged between 18 and 30, with no history or clinical evidence of skin disease or allergy, at the Chemical Defence Establishment, Porton Down (UK).[100] CS crystals were applied (both dry and moistened with two drops of saline) to the skin of the forearm, under a watch glass, for one hour. The test site of subjects was examined at one hour, six hours and subsequently daily. In the dry state, there was no skin irritation, erythema or vesication, in any group of six subjects tested at concentrations of 2, 5, 10 and 15 mg. At 20 mg, there was slight skin irritation in all three subjects tested, while at 25 mg, slight skin irritation was observed in three of seven subjects. In the wet state, slight skin irritation and erythema were observed in all four subjects tested at 10 mg. Mild skin irritation and erythema were observed in all four subjects at 20 mg, in three of seven subjects at 25 mg and in all four subjects at 30 mg (although only three showed erythema). Skin irritation commenced up to 30 minutes following application and disappeared following its removal. Skin erythema lasted for up to one to two days. No residual pigmentation or blanching of the skin was left. No vesication occurred.

Case Reports / Series

Park et al (1972) reported the case of a previously healthy four month old male infant who developed pneumonitis following prolonged exposure to CS.[101] The infant had been exposed to CS "gas" for two to three hours inside a house where police had fired CS tear gas canisters. On the second hospital day, changes consistent with a first-degree burn were observed on the skin of the malar region.

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[99] Maibach H, Marzulli F (1971). Allergic sensitization potential of riot control lacrimants: Human Draize Test. Contact Dermatitis 9: 209. ID 27280

[100] Holland P, White R (1972). The cutaneous reactions produced by o-chlorobenzylidenemalononitrile and chloroacetophenone when applied directly to the skin of human subjects. Br J Derm 86: 150-54. ID 26877

[101] Park S, Giammona S (1972). Toxic effects of tear gas on an infant following prolonged exposure. Amer J Dis Child 123: 245-6. ID 26869.

Gollhausen et al (1988) reported seven patients with skin reactions after exposure to tear gas.[102] These patients were patch-tested with CS and chloroacetophenone (CN). One patient was found to have an allergic contact dermatitis to both CS and CN. Four patients were diagnosed with toxic contact dermatitis from CS. CS-induced toxic contact dermatitis can show a delayed appearance.

Ro and Lee (1991) presented two young women who developed allergic contact dermatitis due to CS, confirmed by skin patch tests.[103] One case developed eczema on the cheeks and neck within one day of exposure and this lasted about seven days [although required systemic corticosteroids for four days]. The other case developed eczema on the face and forearms within four hours of exposure and this lasted about two days. The eczema consisted of an erythematous vesicular eruption. Both cases had been previously exposed to CS "gas" due to political demonstrations in Seoul and had no previous history of eczema from this.

Parneix-Spake et al (1993) presented a case series of 11 patients hospitalised in a Paris university hospital, over a three-year period with bullous dermatitis, after having been sprayed with CS.[104] Five cases had previous exposure to self-defence sprays. The clinical picture involved an erythematous dermatitis localised on areas directly exposed to the spray (face, neck and hands) or reached by the agent flowing along the body (shoulders and trunk). Vesicles, blisters and crusts were present. The dermatitis began between 12 hours and three days after exposure. Seven cases had associated swelling of the face and three cases had keratitis (out of nine that had an ophthalmologic examination). The extent of the body surface involved varied from 2% to 13%, with an average of 8%. The mean duration of hospitalisation was six days. The severity or timing of the disease in the five cases previously exposed to CS did not differ from the other cases. The authors considered that this finding suggested that the dermatitis was irritant in nature rather than allergic. Although allergic dermatitis could not be definitely excluded as patch tests were not performed.

Kanerva et al (1994) presented a series of patients with allergic contact dermatitis from single exposure to a chemical, seen at a Finnish dermatology clinic.[105] One patient was a 36-year old male with no personal or family history of atopy exposed to 2.5% CS spray on his face, neck, chest and arms while being arrested by police. He had no previous exposure to CS. Seven days after exposure he presented for treatment of a red, swollen bullous dermatitis on exposed areas. Oral prednisolone for two weeks healed the lesions. Patch testing to CS, at a concentration as low as 1: 1,000,000, provoked an allergic reaction. The authors argued that these substances, including CS, were strong allergens.

Anderson et al (1996) reported on a case series of 184 people exposed to CS "gas" at a Vietnamese detention centre in Hong Kong and who complained of symptoms

[102] Gollhausen R, Holzmann H, Ring J (1988). Contact dermatitis through tear gas. Munch med Wschr 39: 680-2. ID 27082. English abstract only

[103] Ro YS, Lee CW (1991). Tear gas dermatitis - allergic contact sensitisation due to CS. Int J Derm 30: 576-7. ID 26789.

[104] Parneix-Spake A, Theisen A, Roujeau J, et al (1993). Severe cutaneous reactions to self-defense sprays. Arch Dermatol 129: 913.

[105] Kanerva L, Tarvainen K, Pinola A, et al (1994). A single accidental exposure may result in a chemical burn, primary sensitization and allergic contact dermatitis. Contact Dermatitis 31: 229-235. ID 27234.

consistent with the effects of CS within 21 days of the incident.[106] The time to first presentation to a clinic physician ranged from < 1 day to 19 days (mean 5 days). Mild itching and rash was present in 6% of patients. Ten patients had contact dermatitis. 52% of patients had evidence of first degree- (16 patients), second degree- (78 patients) or third degree- burns (22 patients). The majority of burns were on the arms and legs, but a small number were on the abdomen, chest or back. Many of the burns had a "peppered" appearance and were sustained on areas of skin covered by clothing. Only four patients gave a history of direct contact with hot tear gas canisters. Many of these burns healed with keloid scarring and some disfigurement. Zekri et al (1995) also wrote an article about these 96 cases with acute burns.[107] These cases were seen at the Red Cross Clinic as well as the Burns Centre. These burns were categorised as minor burns, with the total body surface area ranging from 1% to 8%. According to the history and the clinical presentation collected from the patients, the burn injuries were classified into 44 cases of flame burns, 39 cases of contact burns and 13 cases of chemical burns. The flame burns were caused by the fire resulting from the explosion of tear-gas grenades near the victims. The contact burns occurred when the hot canisters touched the patients' bodies. Chemical burns were caused by the effect of the CS powder inside the canisters. These chemicals splashed the nearby patients' clothes and their skin by contact. Examination of those who had chemical burns resulted in eye irritation of the treating medical staff and traces of white powder were evident at the burn sites and on contaminated clothing. One patient was a 5-year old boy who sustained a 4% chemical burn that involved the hand and thigh. This patient required debridement and skin grafting of a 7cm by 5cm deep burn of the thigh. Three patients presented at two weeks post-injury with raised hypergranulation tissue and another five patients were followed for hypertrophic scar formation.

Blaho and Winbery (1998) in a letter to the editor of the Lancet asserted the relative safety of chemical batons.[108] They were physicians who worked at an emergency department in inner city Memphis that treated many patients under arrest that had been restrained by chemical batons. They noted that local police used a formulation of an equal mixture of CS and oleum capsicum (OC) in two different concentrations (5% and 10% spray). They admitted that they did rarely see sprayed patients with contact dermatitis severe enough to warrant treatment with oral antihistamines or corticosteroids. There was no comment concerning the duration of the contact dermatitis in these patients.

Sommer and Wilkinson (1999) reported the case of a 24-year old male with allergic contact dermatitis to CS aerosol that required treatment at a Leeds hospital, UK.[109] The patient was detained by police and CS "gas" used. The patient developed an immediate irritant skin reaction that improved. Six days after CS exposure, the patient developed a bullous dermatitis with extensive oedema and blistering. This was still present 10 days after CS exposure and the patient required topical and oral steroids.

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[106] Anderson P, Lau G, Taylor W, et al (1996). Acute effects of the potent lacrimator o-chlorobenzylidene malononitrile (CS) tear gas. Human and Experimental Toxicology 15: 461-5. ID 26803.
[107] Zekri A, King W, Yeung R, et al (1995). Acute mass burns caused by o-chlorobenzylidene malononitrile (CS) tear gas. Burns 21(8): 586-9. ID 27772
[108] Blaho K, Winbery (1998). Re: Safety of chemical batons. (Letter to Editor). Lancet 352: 1633. ID 26771
[109] Sommer S, Wilkinson S (1999). Exposure-pattern dermatitis due to CS gas. Contact Dermatitis 40: 46-7. ID 26794.

He had a previous exposure to CS but no history of skin disease or atopy. Histology showed spongiotic dermatitis with many eosinophils, consistent with an acute contact dermatitis. Patch testing was not performed as the patient was lost to follow-up. The CS formulation used was 5% CS in methylisobutylketone.

Hill et al (2000) presented a case of a 30-year old Hispanic male prison inmate with persistent, multisystem, hypersensitivity reaction after being heavily "sprayed" and subsequently treated at a Brooklyn hospital.[110] The head, neck, arms and possibly chest were directly sprayed. Over the next day, the subject developed a dry cough, erythema of the exposed skin, swelling about the eyes and loss of appetite. Over subsequent days, a generalised pruritic skin rash and dyspnoea and chest discomfort evolved. Eight days after exposure, he was hospitalised and physical findings included generalised erythema of the skin with fine scaling and excoriations, injected and mildly icteric conjunctivae, respiratory distress and diffuse chest rhonchi. Chest x-ray demonstrated patchy consolidation of left lower lobe and markings at right base. Liver function tests were definitely elevated as was the eosinophil count. A punch biopsy of the skin showed diffuse spongiosis, superficial lymphohistiocytic infiltrate with eosinophils, and focal necrosis of keratinocytes (spongiotic lichenoid dermatitis). Allergy skin testing demonstrated atopy, with reactions to cat, house dust mite, grass and ragweed. Symptoms responded to prednisone but recurred off therapy. The subject continued to complain of cough, dyspnoea and wheezing, provoked by exertion and exposure to cold air, a year following the exposure, while the dermatitis took 6 to 7 months post exposure to resolve. Patch testing after the dermatitis had resolved demonstrated positive reactions at 48 hours to all dilutions of CS and a lesser response to CN. The subject had a previous medical history of allergic rhinoconjunctivitis and occasional inhalation of marijuana, cocaine and heroin in the past. A diagnosis of hypersensitivity reaction with bronchoconstriction, pneumonitis, dermatitis and hepatitis was made. The persisting asthma-like disorder was considered to meet the diagnostic criteria for reactive airways dysfunction syndrome. The chemical spray involved was considered to be CS based on the marked sensitisation observed and purchase records from the prison.

Varma and Holt (2001) presented the case of a 30-year old male hospitalised in Wales for five days with a severe skin reaction after being sprayed with 5% CS in MIBK.[111] The patient was sprayed on the face with CS while in a car (confined space). Pain and swelling of the face and periorbital oedema developed within 6-8 hours after the exposure and the patient sought hospital treatment two days after exposure. Examination showed severe facial erythema and oedema, vesiculation, suppuration and crusting. Swabs from the left ear grew Streptococcus group G and Staphylococcus aureus. Treatment included intravenous antibiotics and oral prednisone. The patient had been exposed to CS spray nine months previously without any skin reaction. He had a past history of psoriasis and depression, was a daily smoker and alcohol drinker. The exact nature of the skin reaction was a little uncertain, either an irritant contact dermatitis or an allergic reaction was thought likely. The long-term sequela was unknown as the patient did not attend for follow-up.

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[110] Hill A, Silverberg N, Mayorga D, et al (2000). Medical hazards of the tear gas CS. Medicine 79: 234-40. ID 23851.
[111] Varma S, Holt P (2001). Severe cutaneous reaction to CS gas. Clinical and Experimental Dermatology 26: 248-250. ID 27422

Southward (2001) described a 20-year old male patient treated for superficial burn at the accident and emergency department of a British hospital after exposure to CS spray.[112] The subject presented 36 hours after he had been sprayed in the face with CS spray for an excessive time. Examination revealed erythema of the scalp and skin of the eyebrows, an eczema-like area on the chin and a superficial burn behind the right ear. The patient failed to attend for follow-up.

Surveys

Shmunes and Taylor (1973) conducted a survey of 28 male employees, aged 21 to 51 years, who worked with CS in a New Jersey plant that had manufactured CS2 for the US government for approximately 11 years.[113] The plant was investigated after eight cases of dermatitis in workers at the plant were reported to the state occupational health program. Each subject was questioned about dermatological problems during their employment, examined by a dermatologist and given 48-hour occlusive patch testing to solutions of CS prepared from crystalline CS diluted 1:1,000, 1:10,000 and 1:100,000 in olive oil. 48- and 72-hour readings of patch test sites were performed. 25 of 28 subjects (89%) had a history of cutaneous reactions to CS. 13 of the current employees had been compensation cases that required visits to the physician. The sites affected were wrist - 18, neck - 14, forearms - 5, chest -3, ears -2, abdomen -2, arms -2, legs -1, forehead -1 and generalised - 1 case. The onset of the first episode of dermatitis occurred following employment in the CS area within two weeks in one subject, two weeks to one month in 12 subjects, two to six months in 10 subjects and seven months to one year in two subjects. The onset of the dermatitis occurred in warm weather in 21 of the 25 subjects with dermatitis. The frequency of the dermatitis was a single episode in eight subjects, two episodes in three subjects, three episodes in four subjects, four or five episodes in four subjects and greater than six episodes in six subjects. 20 of the 25 subjects with dermatitis had no personal or family history of atopy. Physical examination revealed that nine subjects had dermatitis and seven of these had an acute vesiculobullous contact dermatitis to CS. The clinical course consisted of immediate stinging and burning after exposure to CS, erythema was variably present by the end of the work shift and sharply defined and tender by 24 hours and by 48 hours vesicles had joined to form tense bullae. The bullae would break, leaving an erosion that crusted and slowly healed over the following two weeks. Variable postinflammatory hyperpigmentation was left. One subject with a personal history of atopy was observed to have chronic eczema on the neck, which had been present for several months. Two of 25 subjects patch-tested, showed skin reactions consistent with allergic sensitisation to CS (at 1:1,000 solution). Air sampling within the plant found that three areas exceeded US Department of Labour standards (0.4 mg per cubic metre). The highest level (12.0 mg per cubic metre) was obtained during the filling of plastic bags with CS. Workers at this plant did wear protective measures such as uniforms, gloves, boots, and gas masks. Three workers who worked with CS at the plant did not participate in the study.

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[112] Southward R (2001). Cutaneous burns from CS incapacitant spray. Med Sci Law 41: 74-77. ID 27440

[113] Shmunes E, Taylor J (1973). Industrial contact dermatitis. Arch Dermatol 107: 212-216. ID 26875

Carcinogenicity

DNA Binding

Since CS is known to react with the SH-groups of proteins and amino groups such as lysine it was considered possible that it would react with DNA. In a DNA binding study, no CS binding to rat DNA was detected (von Daniken et al 1981).[114] Therefore, possible binding of CS to DNA was at least 100,000 times lower than that of the strong hepatocarcinogen aflatoxin B1 and 4,000 times lower than that of vinyl chloride (von Daniken et al 1981).[115]

Mutagenicity and Carcinogenicity

Mutagenicity refers to the ability to induce a permanent transmissible change in the genetic material, usually in a single gene. Clastogenic means the ability to induce chromosomal breakage. CS has been tested in a variety of in-vitro systems. The most important findings are:

(i)   that CS is clastogenic in-vitro, causing chromosomal damage (NTP, 1983; Bauchinger and Schmid, 1992).[116] [117]

(ii)   that in-vitro, CS can damage the mitotic spindle which is necessary for separating chromosomes when cells divide (Schmid and Bauchinger, 1989; 1991; Ziegler-Skylakakis et al., 1989; Salassidis et al., 1991; Nusse et al., 1992; Miller and Nusse, 1993; Weller et al., 1995).[118] [119] [120] [121] [122] [123] [124]

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[114] Von Daniken A, Friederich U, Lutz W, et al (1981). Tests for mutagenicity in salmonella and covalent binding to DNA and protein in the rat of the riot control agent o-chlorobenzylidene malononitrile (CS). Arch Toxic 49: 15-27. ID 26798

[115] Von Daniken A, Friederich U, Lutz W, et al (1981). Tests for mutagenicity in salmonella and covalent binding to DNA and protein in the rat of the riot control agent o-chlorobenzylidene malononitrile (CS). Arch Toxic 49: 15-27. ID 26798

[116] National Toxicology Program. Toxicology and carcinogenesis studies of CS2 (94% CS) in rats and mice. US National Toxicology Program Technical Report No. 377 (1990). ID 27114

[117] Bauchinger M, Schmid E (1992). Clastogenicity of 2-chlorobenzylidene malonitrile (CS) in V79 Chinese hamster cells. Mutation Research 282: 231-4. ID 26807

[118] Schmid E, Bauchinger M, Ziegler-Skylakakis K, et al (1989). 2-chlorobenzylidene malonitrile (CS) causes spindle disturbances in V79 Chinese hamster cells. Mutation Research 226: 133-6. ID 26813

[119] Schmid E, Bauchinger M (1991). Analysis of the aneuploidy inducing capacity of 2-chlorobenzylidene malonitrile (CS) and metabolites in V79 Chinese hamster cells. Mutagenesis 6: 303-5. ID 26927

[120] Ziegler-Skylakakis K, Summer K, Andrae U (1989). Mutagenicity and cytotoxicity of 2-chlorobenzylidene malonitrile (CS) and metabolites in V79 Chinese hamster cells. Arch Toxicol 63: 314-9. ID 26802

[121] Salassidis K, Schmid E, Bauchinger M (1991). Mitotic spindle damage induced by 2-chlorobenzylidene malonitrile (CS) in V79 Chinese hamster cells examined by differential staining of the spindle apparatus and chromosomes. Mutation Research 262: 263-6. ID 26814

[122] Nusse M, Recknagel S, Beisker W (1992). Micronuclei induced by 2-chlorobenzylidene malonitrile (CS) contain single chromosomes as demonstrated by the combined use of flow cytometry and immunofluorescent staining with anti-kinetochore antibodies. Mutagenesis 7: 57-67. ID 27096

[123] Miller B, Nusse M (1993). Analysis of micronuclei induced by 2-chlorobenzylidene malonitrile (CS) using fluorescence in-situ hybridization with telomeric and centromeric DNA probes and flow cytometry. Mutagenesis 8: 35-41. ID 27097

[124] Weller E, Kubbies M, Nusse M (1995). Induction of cell cycle perturbations by the tear gas 2-chlorobenzylidene malonitrile (CS) in synchronously and asynchronously proliferating mammalian cells. Cytometry 19: 334-42. ID 26806

The clastogenic effect appears to be due to CS itself or a short-lived metabolite while the mitotic spindle damage involves the metabolite 2-chlorobenzaldehyde. These damaging effects of CS could result in the daughter cells having too many, too few or damaged chromosomes.

In-vivo studies: There have been two studies in which live mice were exposed to CS and peripheral blood and bone marrow were examined for evidence of chromosomal damage (Wild et al., 1983; Grawe et al., 1997).[125][126] Both studies were negative. Hence the in-vivo studies suggest that CS does not damage chromosomes or interfere with chromosomal segregation when cells divide.

There is considerable reassurance from two carcinogenicity studies in which rats and mice were exposed to inhaled CS for 6 hours a day, 5 days a week for 2 years (US National Toxicology Program Technical Report No. 377).[127] There was no evidence of any increase in tumours in the exposed animals, in particular there was no increase in tumours in the tissues of contact in the mouth and respiratory system.

Overall, the absence of genetic damage in live animals exposed to CS and the negative carcinogenicity studies suggest that CS is unlikely to be carcinogenic in humans.

MIBK and Mutagenicity

One CS formulation also contains the solvent MIBK. This compound has also been examined for mutagenic activity. The results were all negative. It was negative in a series of in-vitro tests and in bone marrow micronucleus assay.[128]

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[125] Wild D, Eckhardt K, Harnash D, et al (1983). Genotoxity study of CS (ortho-chlorobenzylidemalononitrile) in salmonella, drosophila, and mice. Failure to detect mutagenic effects. Arch Toxicol 54: 167-70. ID 26800

[126] Grawe J, Nusse M, Adler I (1997). Quantitative and qualitative studies of micronucleus induction in mouse erythrocytes using flow cytometry. 1. Measurement of micronucleus induction in peripheral blood polychromatic erythrocytes by chemicals with known and suspected genotoxicity. Mutagenesis 12: 1-8. ID 27099

[127] National Toxicology Program. Toxicology and carcinogenesis studies of CS2 (94% CS) in rats and mice. US National Toxicology Program Technical Report No. 377 (1990). ID 27114

[128] Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products, and the Environment (1999). Statement on 2-chlorobenzylidene malononitrile (CS) and CS spray. London: Department of Health, 1999. www.doh.gov.uk/pub/docs/doh/csgas.pdf

Miscellaneous Effects

Bhattacharya and Hayward (1993) reported the case of a previously healthy 19-year old male sprayed in the face with CS "gas", and who also suffered from stab wounds.[129] He underwent abdominal surgery for a stab wound at a Middlesex hospital. However, difficulties in intubating the patient occurred from the anaesthetist experiencing severe blepharospasm and lacrimation from the presence of CS "gas" in the oropharynx.

Barlow (2000) also reported difficulties intubating a 25-year old male patient that required a general anaesthesia for an explorative laparotomy who had been exposed to CS "gas".[130] Police had used CS "gas" to control aggressive behaviour in this patient who had a history of mental illness. The anaesthetist experienced stinging eyes and breathing difficulties during intubation and the insertion of a nasogastric tube.

Anderson et al (1996) reported on a case series of 184 people exposed to CS "gas" at a Vietnamese detention centre in Hong Kong and who complained of symptoms consistent with the effects of CS within 21 days of the incident.[131] The time to first presentation to a clinic physician ranged from < 1 day to 19 days (mean 5 days). At the first visit, 15% complained of a sore throat, which lasted a maximum of 38 days. On clinical examination, 27% of patients had findings consistent with a sore throat. At the first visit, 29% of patients complained of headaches but this complaint was present in only 1% of patients by visit three (at 22-27 days). At the first visit there were complaints of rhinorrhea in about 2% of patients, nausea in 3%, vomiting in 9%, haematemesis in 4% (clinically confirmed in one patient), abdominal pain in 4%, diarrhoea in about 2%, mouth ulcers in 2% (confirmed clinically) and anorexia in about 1%. At the first visit, there were also complaints of dizziness in about 3% of patients, agitation in about 1% and syncope in < 1%.

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[129] Bhattacharya S, Hayward A (1993). CS gas - implications for the anaesthetist. Anaesthesia 48: 896-7. ID 26791.
[130] Barlow N (2000). Letter to the editor. Resuscitation 47: 91-92. ID 27418.
[131] Anderson P, Lau G, Taylor W, et al (1996). Acute effects of the potent lacrimator o-chlorobenzylidene malononitrile (CS) tear gas. Human and Experimental Toxicology 15: 461-5. ID 26803.

OTHER TEAR GAS

Gray (1995), in a letter to the editor, described the ocular effects of a tear gas agent, 1-chloroacetophenone.[132] Ocular irritation typically lasts only 15 minutes but may persist for up to three days. Effects were considered worse if fired at close range as powder infiltration of the conjunctiva, cornea and sclera can occur. Conjunctival tearing may result due to the excessive force. Complications such as corneal stromal oedema, symblepharon, pseudopterygium, infective keratitis, trophic keratopathy, posterior synechia, secondary glaucoma, cataracts, hyphaema, vitreous haemorrhage, and traumatic optic neuropathy may also occur.

Billmire et al (1996) presented the case of a 4-week old healthy male infant exposed to 5% pepper-gas when a self-defence spray accidentally discharged in his face and resulted in toxic pneumonitis with respiratory failure.[133] There was rapid onset of gasping respirations and epistaxis followed by apnea and cyanosis. Mechanical ventilation for respiratory failure was needed about 20 minutes after exposure. The initial chest x-ray showed bilateral diffuse parenchymal infiltrates. Culture of purulent sputum grew Moraxella catarrhalis by day 2 post-injury. Extracorporeal membrane oxygenation (ECMO) was initiated 96 hours post-injury and was need for 138 hours. The infant was discharged home 9 days after ECMO (about 19 days after exposure). In the following 12 months, the infant had three hospital admissions for viral respiratory infections with fever, wheezing and tachypnea. The pepper-gas spray involved was 5% oleoresin capsaicin, a volatile oil derived from red chilli peppers. It is an alkylating agent that results in severe irritation to the skin and mucus membranes. Additional compounds in this spray were the propellants, isobutane and propane and two organic solvents, methyl isobutyl ketone (reported to have caused upper respiratory tract irritation) and tetrachloroethylene (reported to cause pulmonary oedema). The mechanism of action of pepper-gas was through the release of substance P from sensory neurons, resulting in vasodilatation, increased vascular permeability and altered neutrophil chemotaxis. There have been reports of acute bronchospasm and reversible pulmonary oedema after exposure to pepper gas.

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[132] Gray P (1995). Treating CS gas injuries to the eye (Letter). BMJ 311: 30th September.
[133] Billmire D, Vinocur C, Ginda M, et al (1996). Pepper spray induced respiratory failure treated with extracorporeal membrane oxygenation. Pediatrics 98: 961-63. ID 23889.