An assessment of Pepper Spray: Oleoresin Capsicum (OC)

I) What is Oleoresin Capsicum?

Oleoresin capsicum, a mixture of many compounds [1], is obtained by extracting dried, ripe fruit of chili peppers of the genus *Capsicum*, which is a genus of tropical and subtropical herbs and shrubs. They produce Capsaicin (8-methyl-N-vanillyl-6nonenamide), the main compound, and other derivates (Figure 1). The Scoville scale allows to measure the relative heat of peppers and compounds which is shown in Table 1. Many other organic and inorganic compounds can be found, and concentrations vary depending on the manufacturer since it is a product of natural extraction [2].

Source	Scoville Heat Units (HPLC)
Jalapeño pepper	5000
Cayenne pepper	2500-25000
Habanero pepper	85000-200000
Pure capsaicin	15000000
OC (10%)	1500000

Table 1: *Scoville scale of different peppers*

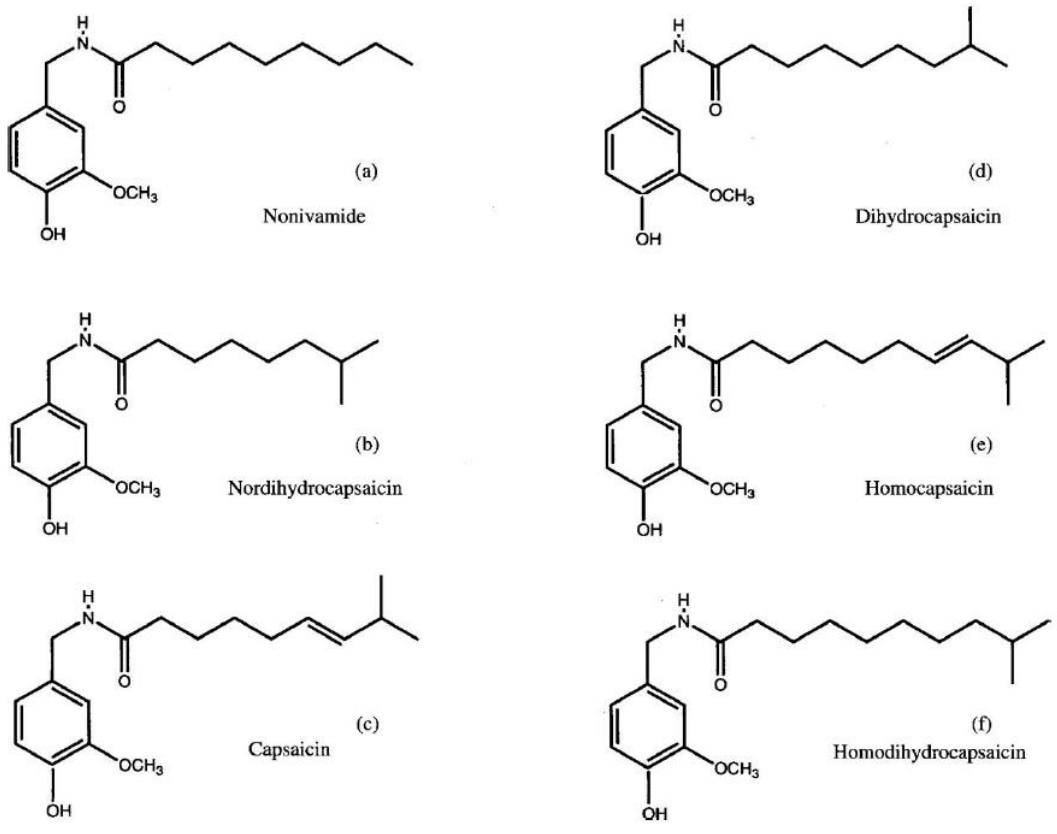


Figure 1: *Chemical structure of Capsaicin (c) which represents around 70% of OC, and other derivates like dihydrocapsaicin (20%), norhydrocapsaicin (7%), homocapsaicin (1%) and monodihydrocapsaicin (1%).*

Historically, using pepper in law enforcement was already a Japanese tradition, where a lacquer or a brass box with a wide mouthpiece was used to blow pepper in the eyes of a person sought to be apprehended. This was called “metsubushi” (Figure 2).

Figure 2: *Metsubushi device*

Nowadays, Capsaicin is used in a concentration of 1% (civilian use) to 10% (law enforcement use) in a solvent that can be water, although Capsaicin is not soluble in water, alcohol which is flammable and already ignited in one described occasion 1, or a non-flammable organic solvent which has its own toxicity.

It is an odourless, pungent tasting off-white solid with a melting point of about 65°C and a boiling point of 210–220°C [3]. It is often considered as the safest tear gas spray, compared to CN or CS [4]. For instance, self-defense spray could not be purchased, possessed, and used in New York State before 1996, and the Department of Health assessed health hazards of those three molecules, concluding OC was the safest after new laws [5].

II) Mechanism of action

Mechanism of action is through interacting with transient potential receptor vanilloid 1 ion channel of Nociceptors to produce the sensation of pain. The exact binding has been described and is shown in Figure 3 [6].

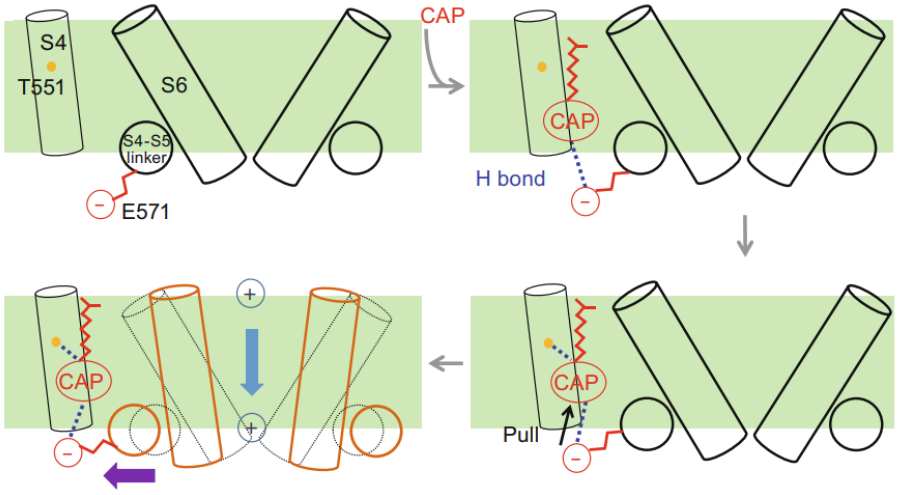


Figure 3: *Summary of TRPV1 activation through capsaicin (CAP) binding.*

TRPV1 opening triggers Calcium influx in the cell, which leads to a pain signal transmission to the brain. Substance P and other neuropeptides, which were conserved in the cell, are also released.

Peripheral release of neuropeptides can affect neurogenic inflammation by vasodilatation, extravasation of plasma proteins and bronchoconstriction. After stimulation, substance P-releasing neurons initiate a number of protective mechanisms in the lung: bronchoconstriction, mucus secretion, cough [7]. There is a broad spectrum of neuronal targets summed up in Table 1 [8].

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

Table 1: *Effects of OC on the nervous system*

Caspaicin excites sensory neurons, but suprathreshold stimulation can result in cell death and cause irreversible damage to the sensory nervous system [9-29]. Sensory neurons with small-diameter unmyelinated afferent processes are mostly targeted [30-38], but this nervous system toxicity is even more widespread with degeneration of cell bodies, axons and nerve terminals [39-42]. Capsaicin could inhibit or abolish transmission of pain in response to various noxious stimuli through neurodegeneration of C-fiber receptors [43]. It was suggested that this effect can be dissociated by using lower doses of capsaicin [44].

It is used to treat painful diseases, through a mechanism that might not involve nerve degeneration, but rather desensitization of the nerve terminal [45]. It is a selective probe to study neurogenic inflammation where stimulation of certain types of sensory neurons produces vasodilatation and extravasation [11, 12, 19, 32, 38, 46-52]. It also has an effect on non-sensory neurons and non-neural excitable cells: inhibition of cardiac muscle excitability [53, 54] inhibition of visceral smooth muscle activity [55, 56] and contraction of vascular smooth muscle [57, 58].

Capsaicin can cause depletion of substance P and other neuropeptides since it triggers their release from primary sensory neurons: neurokinin A (NKA), calcitonin gene-related peptide (CGRP), somatostatin (SOM), and kassinin, as revealed by immunohistochemistry and radioimmunoassay [59-69]. In the absence of substance P, there is no pain sensation [70-74].

Repeated administration of capsaicin produces systemic desensitization to chemogenic and thermal nociceptive stimulation [43, 75-80] desensitization of the airways to chemical irritants and the marked inhibition of vagal bronchoconstriction effects [81]. At high doses, insensitivity to stimuli such as irritants, pain and temperature can become long-lasting [82].

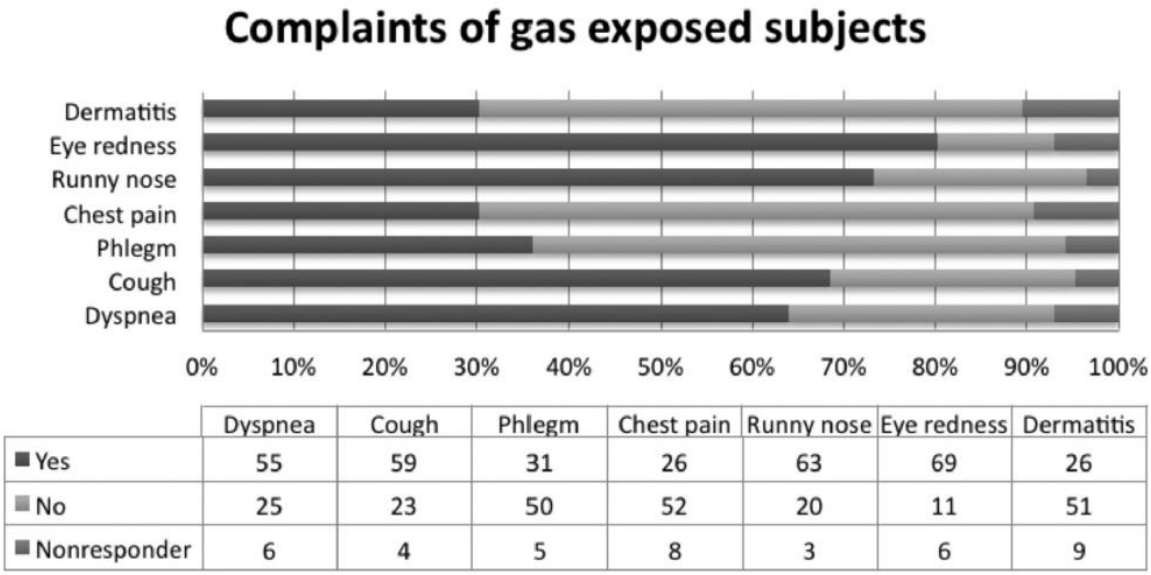
III) Clinical health effects

A retrospective study in Kansas including law-enforcement use of 5% Cap-Stun spray between June 1991 and 1994 reported 81 cases who visited Emergency Department of a total of 908 exposed people. Increased heart rate (40%) and respiratory rate (20%) were observed. Strong effects on the eye were observed, including corneal abrasions (23%). Erythema and burnings were very common (Table 2) [83].

Symptom	Number of patients (81)	Frequency
Ocular	**63**	**78%**
Burning	45	56%
Conjunctival injection	36	44%
Erythema	32	40%
Lacrimation	13	16%
Altered vision	7	9%
Corneal abrasion	7	9%
Dermal	**26**	**32%**
Burning	20	25%
Erythema	12	15%
Respiratory	**6**	**7%**
Shortness of breath	3	4%
Wheezing	2	2%
Cough	1	1%
Throat irritation	1	1%

Table 2: *Frequency of symptoms associated with OC spray exposure*

In Gezi, 2013, civilians were exposed to both CS and OC, and reported similar symptoms (Figure 4) [84].



	Dyspnea	Cough	Phlegm	Chest pain	Runny nose	Eye redness	Dermatitis
Yes	55	59	31	26	63	69	26
No	25	23	50	52	20	11	51
Nonresponder	6	4	5	8	3	6	9

Figure 4: *Complaints of tear gas exposed subjects*

In India, a survey in 294 non-combatant bystanders exposed to OC tear gas showed impressive effects: 97% developed intense irritative cough and irritation of the throat, 84% irritation of the nose and 71% sneezing [85]. 16 developed exacerbations of their underlying respiratory disorders and symptoms were particularly severe and prolonged in children and in people aged 60 years and above. Three children less than 6 years old developed wheezing that required medical attention (Table 3).

Symptom	Number	Frequency
Unpleasant smell	212	72,1%
Cough	286	97,3%
Wheeze	38	12,9%
Chest tightness	107	36,4%
Breathlessness	146	49,7%
Redness of eyes	87	29,6%
Irritation of nose	249	84,7%
Irritation of throat	286	97,3%
Sneezing	208	70,7%
Nasal congestion	104	35,4%
Irritation of skin	89	30,3%
Lacrimation	98	33,3%
Blurring of vision/Blindness	24	8,2%
Sleep disturbance	33	11,2%
Headache	56	19,0%
Nausea	39	13,3%
Vomiting	15	5,1%
Dryness of mouth	67	22,8%
Bitter taste	40	13,6%
Fever	4	1,4%
Worsening of previous respiratory symptoms	16	5,4%
Mood changes	51	17,3%
Nose bleeding	1	0,3%
Hemoptysis	3	1,0%

Table 3: *Symptoms experienced by pacific bystanders at Indian protests*

In an accident in Singapore, OC spray caused 13 casualties reported in Table 4 [86].

	Eye irritation	Throat discomfort	Nausea	Cough	Chest discomfort	Shortness of breath	Skin irritation	Vomiting	Sneezing / runny nose	Giddiness
Male (n=5)	5	2	1	0	1	1	2	1	0	0
Female (n=8)	4	6	3	4	2	1	0	1	2	1
Total % (n=13)	69.2	61.5	30.8	30.8	23.1	15.4	15.4	15.4	15.4	7.7

*There was only 1 paediatric patient, aged 14 months, who presented with cough and vomiting.

Table 4: *Symptoms of the victims*

A ten-year case experience of a poison center control of OC exposure reported that the highest risk factor for severe clinical outcome was exposure during police personal training, in intentional use to incapacitate and in law enforcement situation [87]. 3671 cases were included, and most severe cases represented 1/15th of the total cases. Table 5 shows their symptoms. Non severe effects were self-limiting effects and symptoms; dermal/skin effects including erythema, swelling, pain, and itching; ocular effects including initial pain, tearing, and redness; respiratory effects including initial cough and choking, throat irritation; and gastrointestinal effects including nausea and vomiting.

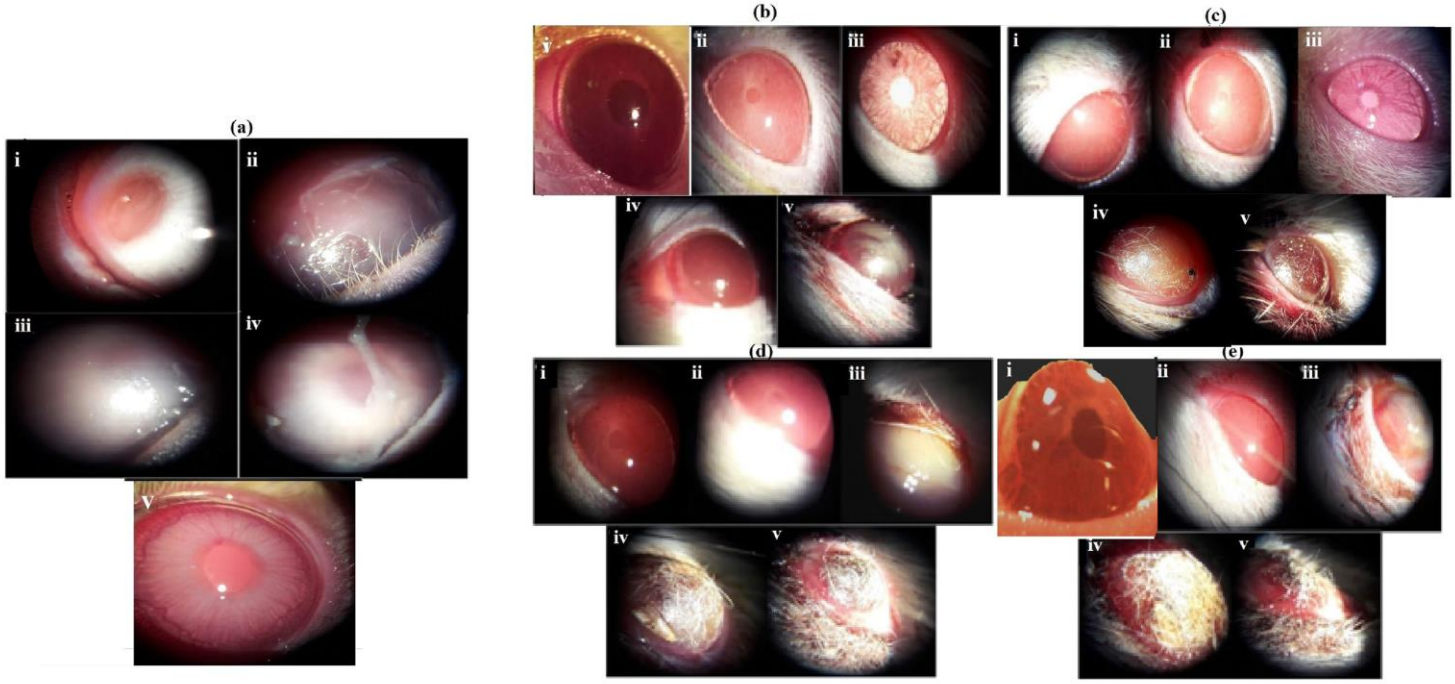
Body/organ system effect	**Associated signs and symptoms**	**n**	**%**
Ocular	Persistent pain, blurred vision, foreign body sensation, discharge or exudate, periorbital swelling	134	53,8%
Respiratory	Shortness of breath, chest tightness, wheezing	79	31,7%
Dermal	Rash, blisters	44	17,7%

Table 5: *Severe symptoms described among the ten-year case experience*

1) Eye

Although it is considered as harmless in the long term, prolonged oleoresin has caused corneal sensory denervation that adversely affected wound healing in animal experimentation [88].

To determine its effects, well controlled experiments have been done on animal models [89] like the bovine, rabbits and rats. Ocular lesions were observed in both rats and rabbits (Figure 5), with histopathologically confirmed nuclear vacuolations and inflammation.

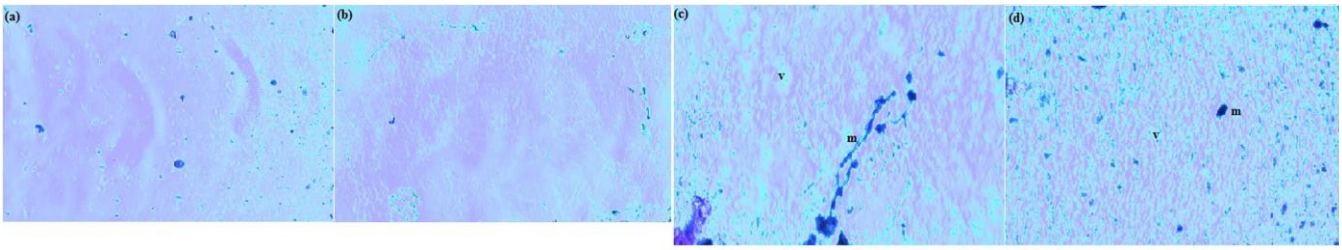


Sl no	Animal species	Capsaicin exposure	GRADING OF OCULAR LESIONS															
			Response after															
			1 hr				24 hrs				48 hrs				72 hrs			
			Cornea	Iris	Conjunctiva	Chemosis	Cornea	Iris	Conjunctiva	Chemosis	Cornea	Iris	Conjunctiva	Chemosis	Cornea	Iris	Conjunctiva	Chemosis
1	Rabbit (*Oryctolagus cuniculus*)	50 mg/ml	3	0	2	2	2	0	1	0	1	0	1	0	1	0	1	0
2			3	2	2	2	2	1	0	1	1	0	1	0	1	0	1	0
3			3	2	2	1	2	0	0	1	1	1	1	0	1	1	1	0
4			3	1	2	2	2	0	1	1	1	0	1	0	1	0	0	0
5			3	2	1	1	2	0	0	0	1	0	0	0	1	1	1	0
6			3	1	2	2	2	1	1	1	1	1	1	0	1	1	1	0

Sl no	Animal species	Capsaicin treatment received	GRADING OF OCULAR LESIONS															
			Response after															
			1 hr				24 hrs				48 hrs				72 hrs			
			Cornea	Iris	Conjunctiva	Chemosis	Cornea	Iris	Conjunctiva	Chemosis	Cornea	Iris	Conjunctiva	Chemosis	Cornea	Iris	Conjunctiva	Chemosis
1	Wistar rats (*Rattus norvegicus*)	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2		25 µg	2 ± 0.6	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0	0	0	0	0	0	0	0	0	0	0	0
3		50 µg	2.6 ± 0.8	1.3 ± 0.5	2.3 ± 0.5	2.1 ± 0.4	1.3 ± 0.5	0	1.1 ± 0.4	0	3.1 ± 0.4	0	2.1 ± 0.6	0	3.8 ± 0.4	0	3.8 ± 0.4	2.1 ± 0.4
4		75 µg	2.6 ± 0.5	1.5 ± 0.5	1.6 ± 0.5	1.8 ± 0.4	2.6 ± 0.5	0	2.1 ± 0.4	1.1 ± 0.2	3.8 ± 0.4	0	2.1 ± 0.4	1 ± 0.0	4 ± 0.0	0	3.6 ± 0.5	2 ± 0.0
5		100 µg	3.5 ± 0.5	2.1 ± 0.4	2.6 ± 0.5	3.1 ± 0.4	3.8 ± 0.4	1.8 ± 0.4	3.1 ± 0.4	2 ± 0.0	4 ± 0.0	0	2.6 ± 0.5	1 ± 0.0	3.8 ± 0.4	0	3.5 ± 0.5	2.1 ± 0.6

Figure 5: *Ocular lesion following OC administration in rabbit eyes (a) either (i) normal and 50 mg/ml capsaicin treated eyes in (ii) 1 hr (iii) 24 hrs (iv) 48 hrs and (v) 72 hrs and rat eyes (b-e) either (i) normal and capsaicin treated (ii) 25 µg/ml, (iii) 50 µg/ml, (iv) 75 µg/ml and (v) 100 µg/ml at 72 hrs after exposure Tables show ocular lesion score*

Corneal opacity was observed in bovine animal model, with cytoplasmic breakdown, vacuolar gaps (v) and corneal mineralization (m) (Figure 6). Inflammation was more predominent in higher doses. Scanning electron microscopy showed some irregularities in treated corneas.



Sl no	Exposure	Opacity	Permeability	IVIS	UN GHS
1	Negative control*	3 ± 0.28	0.00	3 ± 0.28	No category
2	5 mg/ml	18.28 ± 0.12	0.024 ± 0.22	18.64 ± 0.19	No prediction can be made
3	25 mg/ml	19.01 ± 0.09	0.010 ± 0.41	19.37 ± 0.25	No prediction can be made
4	50 mg/ml	19.85 ± 0.31	0.008 ± 0.19	19.97 ± 0.46	No prediction can be made
5	Positive control*	50.22 ± 0.16	1.120 ± 0.34	67.02 ± 0.45	Category 1

Figure 6: *(a) PBS 7.4 and capsaicin treated (b) 5 mg/ml, (c) 25 mg/ml and (d) 50 mg/ml*
The table is summing up the opacity results
IVIS: In Vitro Irritancy Score
UN GHS: United Nations Globally Harmonized System of Classification and Labelling of Chemicals

Tear secretion was reduced in rats exposed to capsaicin, and corneal permeation was induced (Figure 7)

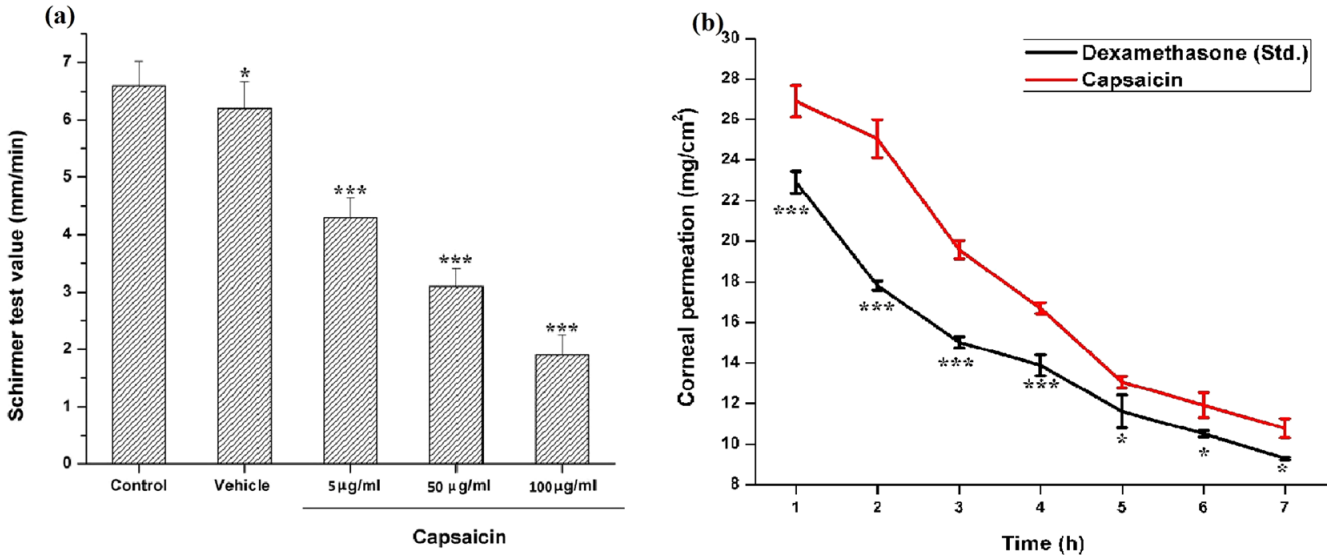
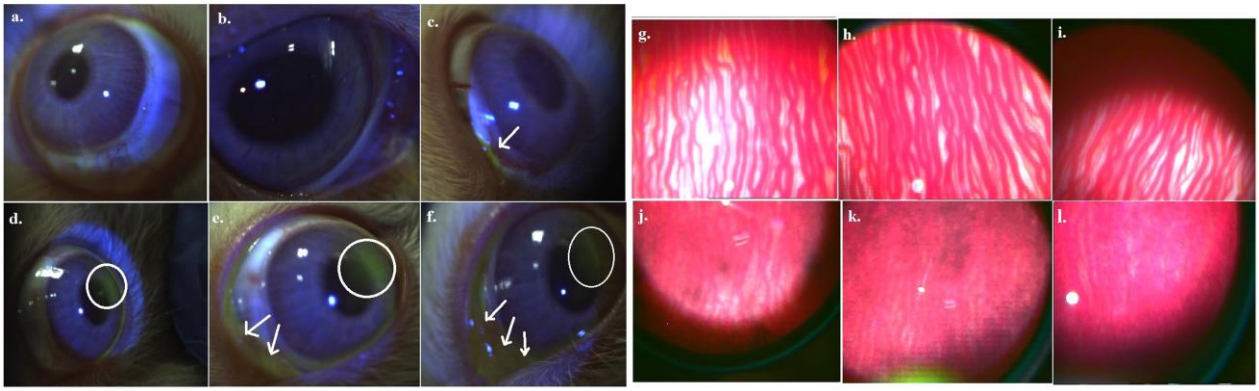


Figure 7: *Schirmer tear secretion (left) with reduced tear production when treated with capsaicin, and corneal permeation due to capsaicin or dexamethasone (positive control) (right)*

Caspaicin also caused fluorescein uptake in the conjunctiva (a-f) of rabbits and vitreous haze with only slight visibility of the blood vessels maybe as a result of vascular inflammatory granulation (g-l) (Figure 8).



Sl no.	Treatments		GRADING OF CORNEAL FLUORESCEIN STAINING (RABBITS) Response after 1 hr Cornea	Nasal conjunctiva	Temporal comnjunctiva	24 hrs* Cornea	Nasal conjunctiva	Temporal comnjunctiva
1	Control		0	0	0	0	0	0
			0	0	0	0	0	0
			0	0	0	0	0	0
2	DMSO		0	0	0	0	0	0
			0	0	0	0	0	0
			0	0	0	0	0	0
3	Capsaicin	25 mg/ml	0	1	0	0	0	0
			0	1	0	0	0	0
			0	1	0	0	0	0
4		50 mg/ml	1	0	0	0	0	0
			1	0	0	0	0	0
			1	0	0	0	0	0
5		75 mg/ml	1	1	0	0	0	0
			1	1	0	0	0	0
			1	1	0	0	0	0
6		100 mg/ml	1	2	0	0	1	0
			1	2	0	0	1	0
			1	2	0	0	1	0

Figure 8: *fluorescein staining (a-f), with results summed up in a table, and ophtalmoscope imaging of the fundus (g-l). (a,g) control (b,h) DMSO exposed (c,i) 25 mg/ml capsaicin exposed (d,j) 50 mg/ml capsaicin exposed (e,k) 75 mg/ml capsaicin exposed (f,l) 100 mg/ml capsaicin exposed.*

The optic nerve was also checked in rats. Conduction velocity was reduced when exposed to capsaicin, which was consistent with scanning electron microscopy showing disruption of spherically arranged neurofilaments of collagen fibers observed at the level of the optic nerve (Figure 9).

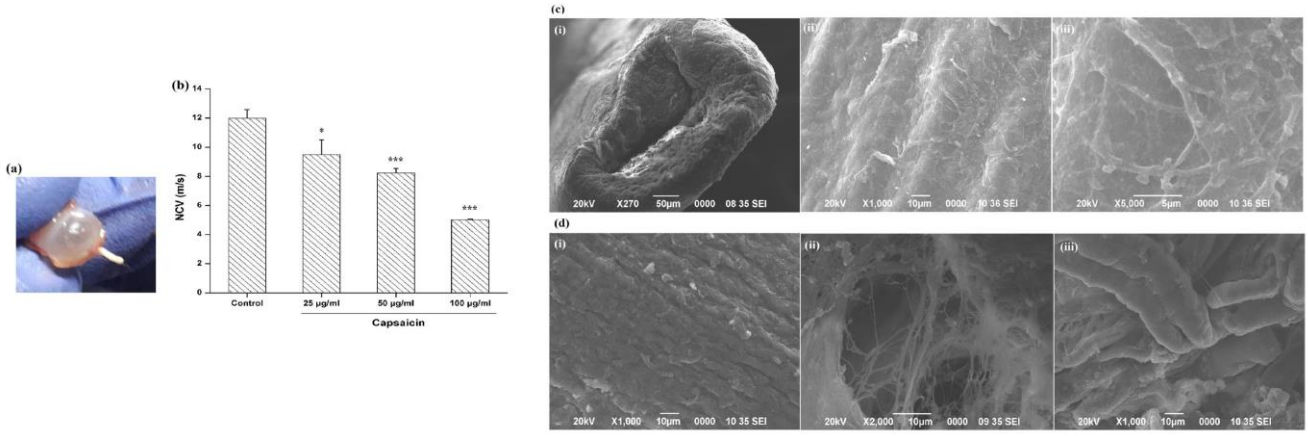


Figure 9: *(a) rat optic nerve, (b) conduction velocity, scanning electron miscroscopy of control (c) and exposed rats (d) optic nerve*

Inflammation was confirmed by measuring cytokines expressed in the optic nerve (Figure 10).

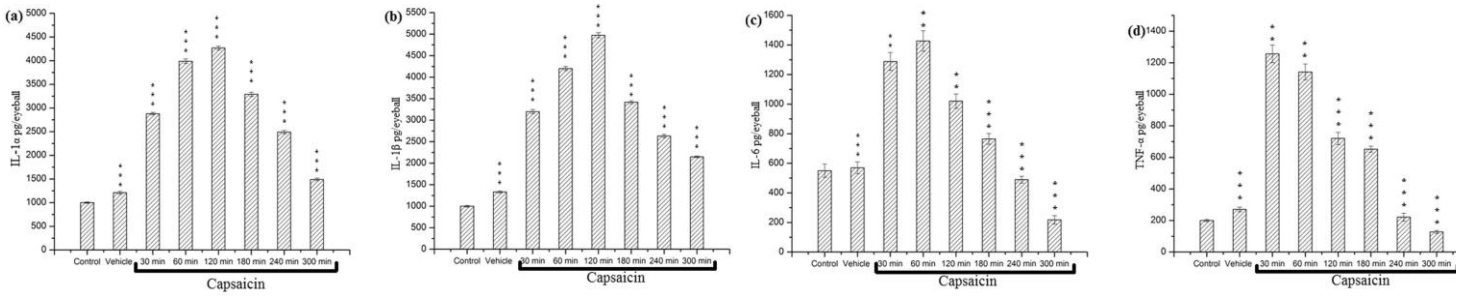


Figure 10: *Enzyme-linked immunosorbant assay (ELISA) of (a) IL-1α (b) IL-1β, (c) IL-6 (d) TNF- α*

A prospective randomized clinical trial on 47 subjects confirmed the well-known symptoms: blepharospasm, tearing, and blurred vision. It can also cause conjunctival inflammation, redness, severe burning pain and swelling. A Cochet-Bonnet aesthesiometer allowed to measure corneal sensitivity. Corneal sensitivity was reduced from normal to almost zero 10 minutes after exposure. One hour after exposure, symptoms were already improving and no long-term effects were observed after one week (Figure 11). Proparacaine hydroxhlorine 0,5% improved symptoms whereas fluribuprofen was inefficient [90].

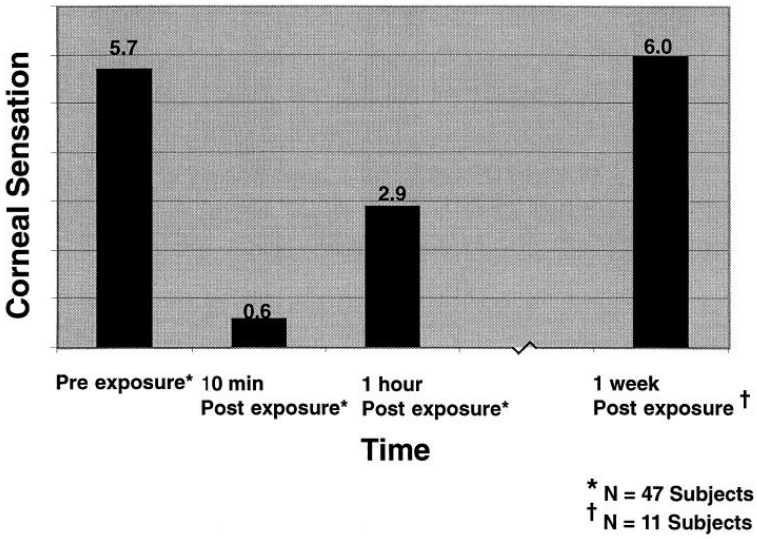


Figure 11: *Corneal sensation of the 47 volunteers 10 minutes, 1 hour and 1 week after exposure*

This finding was confirmed by noncontact esthesiometer measurement in 5 police officer volunteers, which showed chemical sensitivity and cold sensitivity loss, even one week after exposure. Nerve Growth Factor (NGF), which is produced after chemically induced inflammation, was found in tears [91].

Topical application of capsaicin can eliminate the blink reflex for up to 5 days following dosing [30].

In a review of 100 cases in a hospital jail, where a 10% pepper spray was used, 38% had scleral injection and 7% had corneal abrasion, confirming previous results [92].

Systemic administration of capsaicin is associated with trigeminal nerve fiber degeneration in the cornea [93].

After the events in Gezi, Turkey, in 2013, 96 volunteers participated in a Schirmer test, measuring wetness of the eye. 82 subjects wore goggles and were protected whereas 14 did not. 35% of unprotected and 24% of protected subjects had dry eye. This is indicative of sensory denervation, which might indicate long term effects of OC exposure [94].

Conjunctival proliferation was observed after a 2,5-year-old child was exposed to OC pepper spray. This proliferation could be removed with surgery (Figure 12) [95].

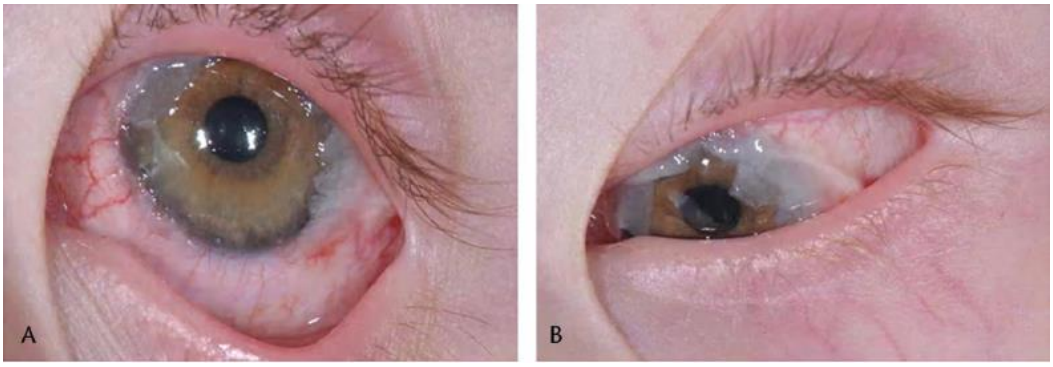


Figure 12: *Conjunctival proliferation of the left eye 3 weeks after exposure*

A patient who was exposed to OC spray showed kerotopathy, inflammation and permanent corneal opacity, observed 5 months after exposure [96].

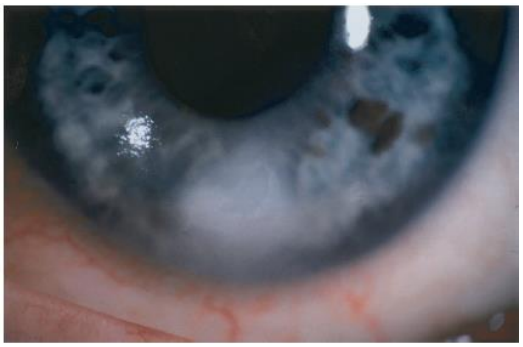


Figure 13: *Slit-lamp photograph 13 days after initial injury, showing smoldering stromal inflammation with overlying epithelial defect.*

Four cases of corneal erosion have been described in Finland [97]. The first one (Figure 14) had signs of necrosis in his left nasal conjunctiva with corneal erosion three days after exposure to 5% OC spray.

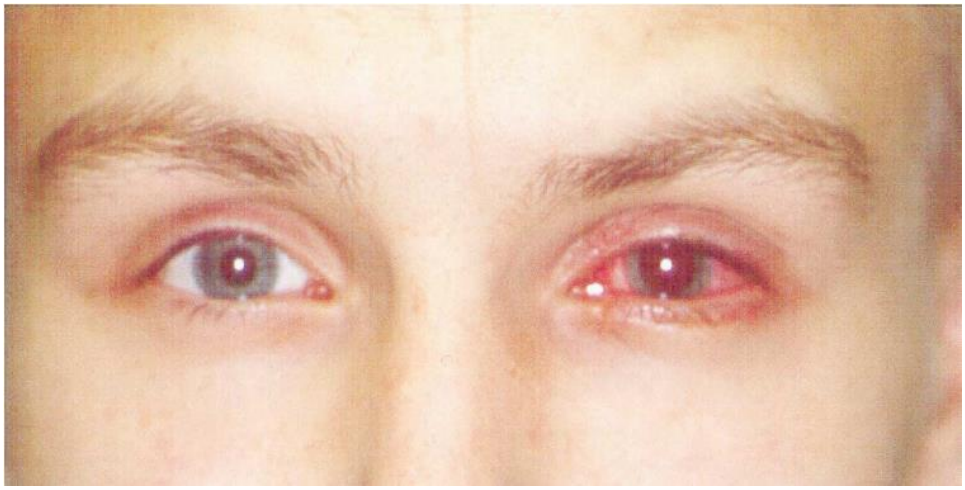


Figure 14: *Patient 1, 3 days after OC exposure*

The second case had conjunctival necrosis the corneal epithelium was entirely damaged (Figure 15). He still felt effects 11 days after exposure, with erosions on the left eye and a streak-like scar on the right eye.

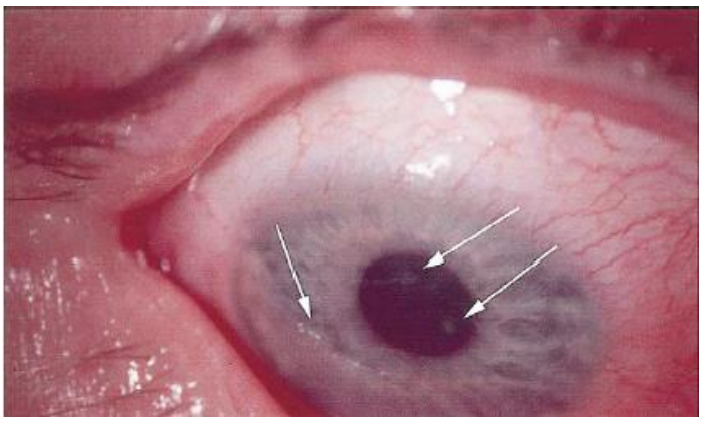


Figure 15: *Patient 2, presenting erosion and stromal opacities (arrows)*

The third case was a security agent, who was sprayed with a mock spray during a training session. Interestingly, it did not contain any OC, but was filled with the solvent, 92% trichlorethylene. The erosion resolved two days later.

The last patient did not rinse after exposure to an unidentified Russian OC spray. He presented chemical burns, photophobia, conjunctival hyperemia, chemosis and an 80% epithelial defect on the right. Three weeks later, his vision went back to normal but his corneal epithelium was rough with punctuate staining with fluorescein and corneal sensitivity was lost. Nerve damage was observed six weeks after exposure, associated with the formation of a scar and keratocyte activation (Figure 16).

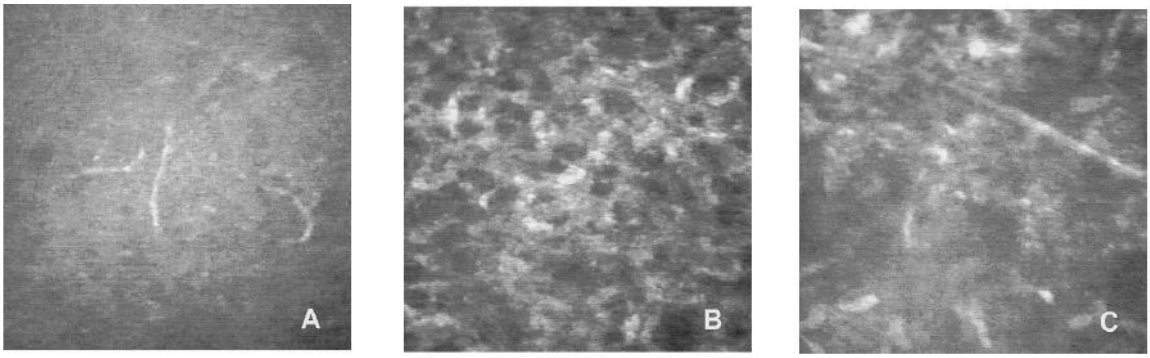


Figure 16: *Patient 4, in vivo confocal microscopic images of a cornea at week 6*
(A) Short nerve fiber bundles posterior to the basal epithelial cells.
(B) Intense scarring with activated keratocytes.
(C) A stromal nerve was observed with activated keratocytes and haze formation.
Size of each image is 235 x 235 µm.

For demonstration purpose, a plastic cup was exposed to OC tear gas and melted with holes appearing after 4 minutes, and a contact lens hardened and stained red-brown.

Figure 17: *Hole in a plastic cup (left) and hardened stained contact lens (right) after OC*

Two cases of extensive ischemia to the limbus and the conjunctiva and a circular conjunctival chemosis were diagnosed due to a 2,6% OC spray. On the long term, superficial keratitis, a reduced corneal sensibility and in one case deep stromal scarring remained (Figure 18) [98].

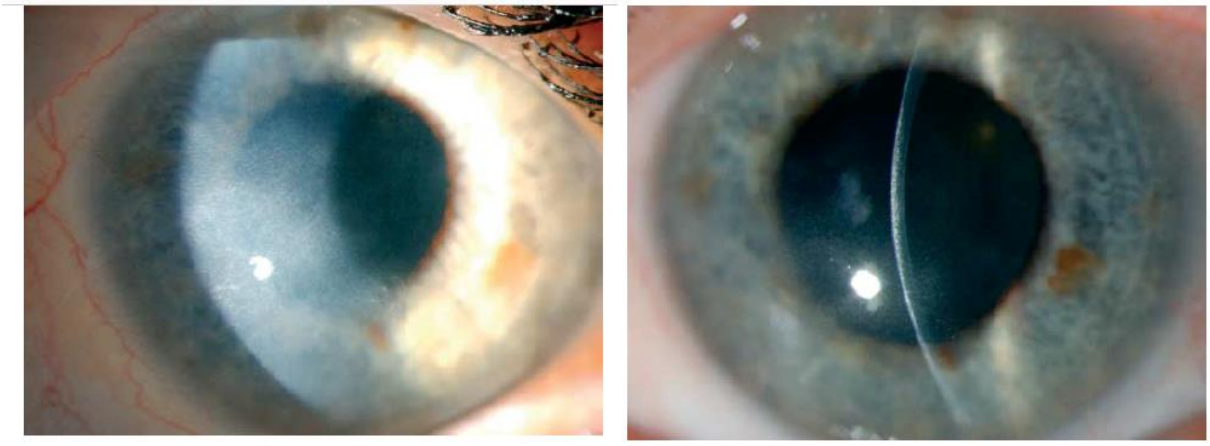


Figure 18: *Scar and loss of sensitivity observed 7 months (left) and 10 months (right) after exposure to 2,6%*

In a 49-year-old subject exposed to OC spray, corneal erosion was followed by necrosis one day later. There was limbal stem cell deficiency 4 weeks later and conjunctivalisation after 6 months (Figure 19) [99].

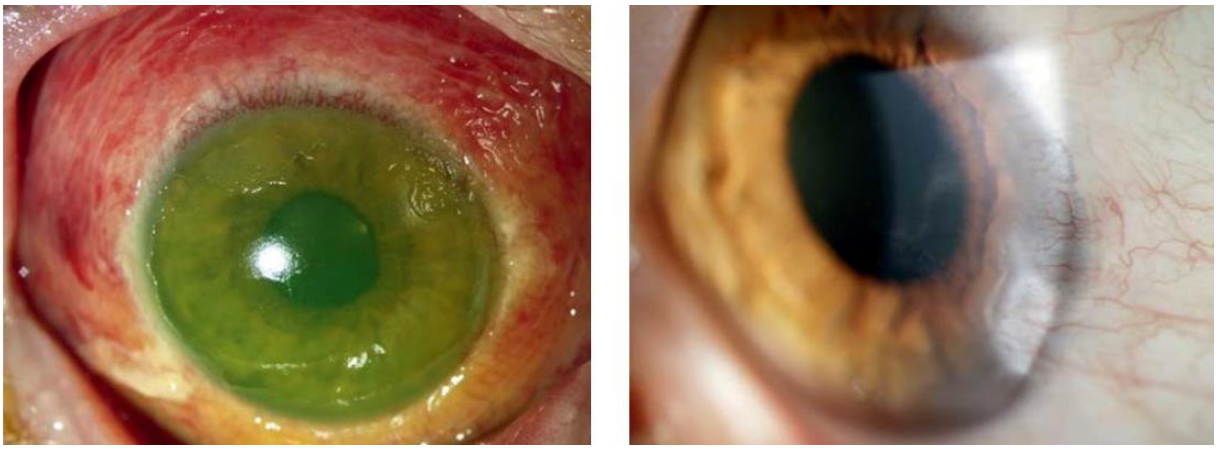


Figure 19: *Chemical burn with OC caused necrosis after one day (left) and conjunctivalisation (right) 6 months*

2) Skin

OC causes a sensation of burning pain, tingling, edema, erythema and occasionally blistering on the skin [100, 101]. In prolonged exposure, persistent dermatitis (Figure 20) can also occur. It can enhance inflammation like allergic dermatitis [102]. It was postulated that the mechanism involved in inflammation was due to release of substance P by the skin cells after OC exposure. In fact, it has been reported to deplete the skin of a variety of biochemical constituents like substance P, somatostatin, prostaglandin and acetylcholine [30].

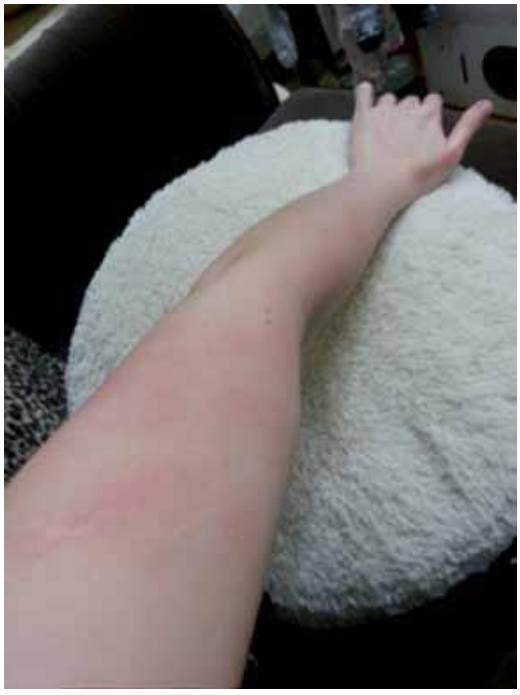


Figure 20: *Dermatitis four hours after exposure to OC spray*

3) Respiratory system

In animal experimentation, OC induced an increase in mucus secretion in the trachea and interstitial edema in the lung (Figure 21) in male wistar rats [103].

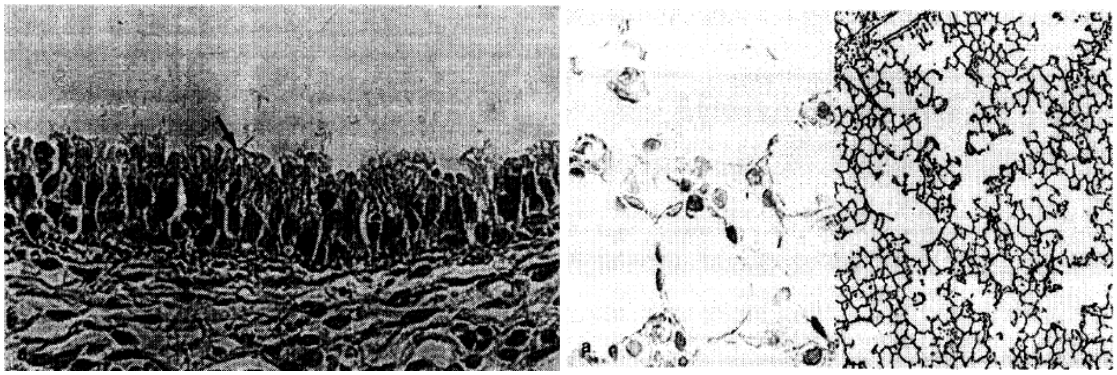


Figure 21: *Increased mucus secretion in the trachea (left) and interstitial edema in the lung (right)*

Inflammation markers like IL-l and TNF-a was observed in serum of blood in female rats, with pulmonary presence of reactive oxygen intermediates and infiltration of polymorphonuclear leukocytes [104].

Tracheal epithelium ciliary beat frequency (CBF) was measured after exposure to OC or CS in 6 mice. Ciliary beats are involved in trapping particles in the surface liquid that covers the airway epithelium and clearing them from the tracheobronchial tree [105]. At commonly used doses of OC, ciliary beats are totally blocked, and therefore, lower concentrations were used to measure ciliary beat reduction. It had been shown that CBF was increased at very low doses (10^{-9} M), this effect was reduced when the concentration was raised until it had no effect at 10^{-6} M [106]. The mechanism involved was studied and showed that this increase in CBF was due to release of substance P consequently to capsaicin exposure [107]. But when the concentrations get higher, CBF is reduced.

This effect is very similar to that of bronchodilatation at high doses of capsaicin (10^{-4} M) [108], whereas lower doses ($3x10^{-9}$ M) cause bronchoconstriction similar to that of smokers or asthmatics [109].

CBF reduction due to OC exposure could be countered by ATP addition, which is known to enhance CBF by triggering a transmembrane Ca^{2+} influx [110]. Cyclooxygenase (COX) pathway, also involved in CBF, was tested with indomethacin pre-treatment, which is a COX inhibitor. This did not alter OC effect on CBF. The guanylate cyclase–dependent pathway was also assessed using an inhibitor, methylene blue. In this case, OC effect on CBF was inhibited. CBF reduction is also related to protein kinase C activity, since its action could be blocked by a PKC inhibitor, H-7 (Figure 22) [111].

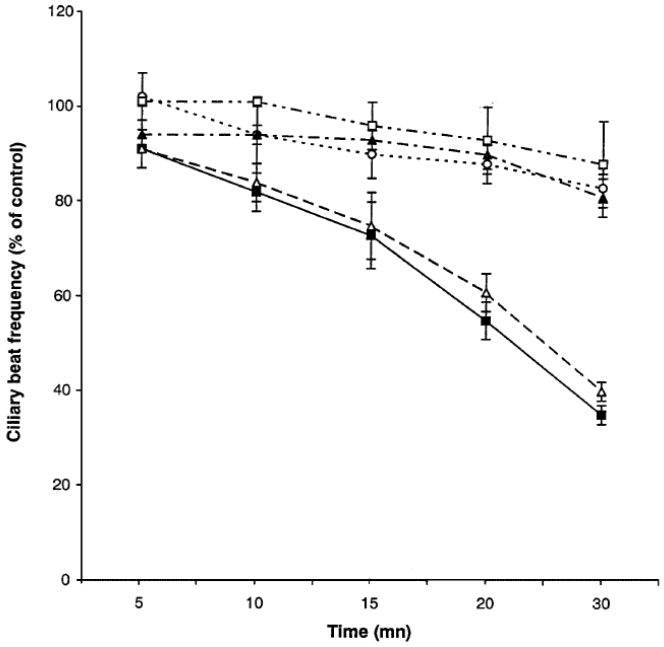


Figure 22: *Effects of 0,05% OC alone (closed squares) and after pretreatment of 15 min with ATP (10^{-4} M, open squares), indomethacin (3×10^{-6} M, open triangles), methylene blue (10^{-5} M, closed triangles), and H7 (10^{-5} M, open circles) on ciliary beat frequency (CBF) in mouse tracheal epithelium.*

Responses are expressed as percentages of baseline CBF obtained before pretreatment. Each point represents the mean S.E. of six experiments.

The respiratory rate is reduced after inhalation of OC dispersed as a gas in mice (Figure 23) [112, 113]. Expiration is prolonged, indicating sensory irritation. The consequence is a reduction in respiratory rate by 55-60%.

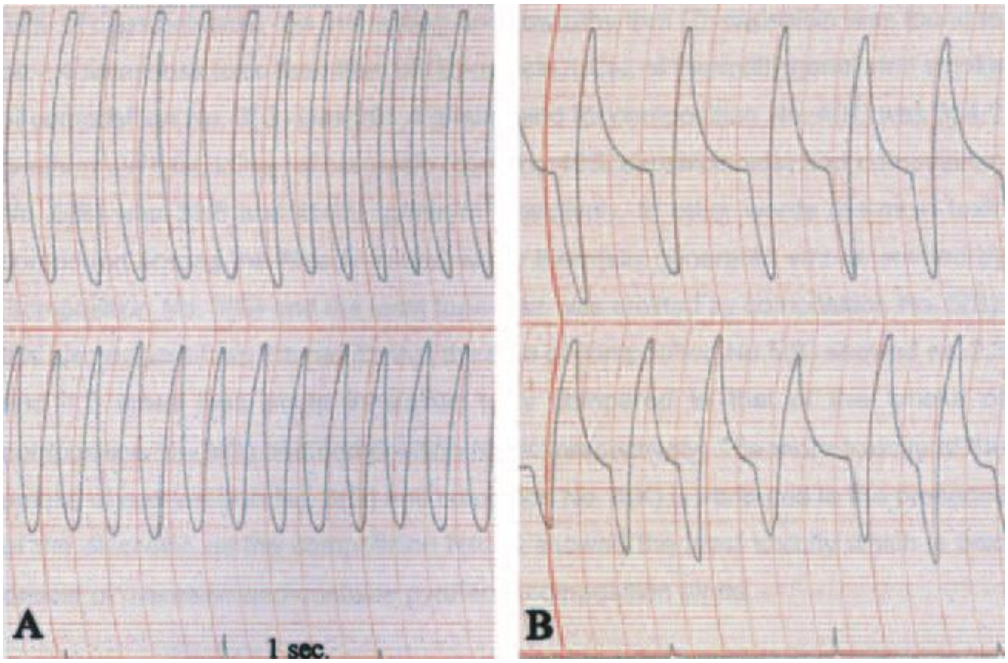


Figure 23: *Inspiration (upwards defection) and expiration (downwards defection) measured in mice exposed to acetone alone (A, which was identical to no exposure control) and after exposure to OC smoke at 55.65 mg/m^3 (B).*

Capsaicin also activates protective reflexes to avoid access of irritant material to lower airways [30, 36, 114] such as avoidance, sneezing, coughing and apnea and rapid shallow breathing in response to airway irritation [59, 115-117]. It is associated with increased vascular permeability to plasma proteins in the airway mucosa [118].

In the nasal passages, activation of capsaicin sensitive sensory nerves results in profound vasodilation, secretion, and increased nasal mucosal volume. Nasal mucosa was damaged in animal experimenting on rats exposed to OC. Exposure time and exposure level were independently influencing nasal mucosal damage, up to creating holes [119].

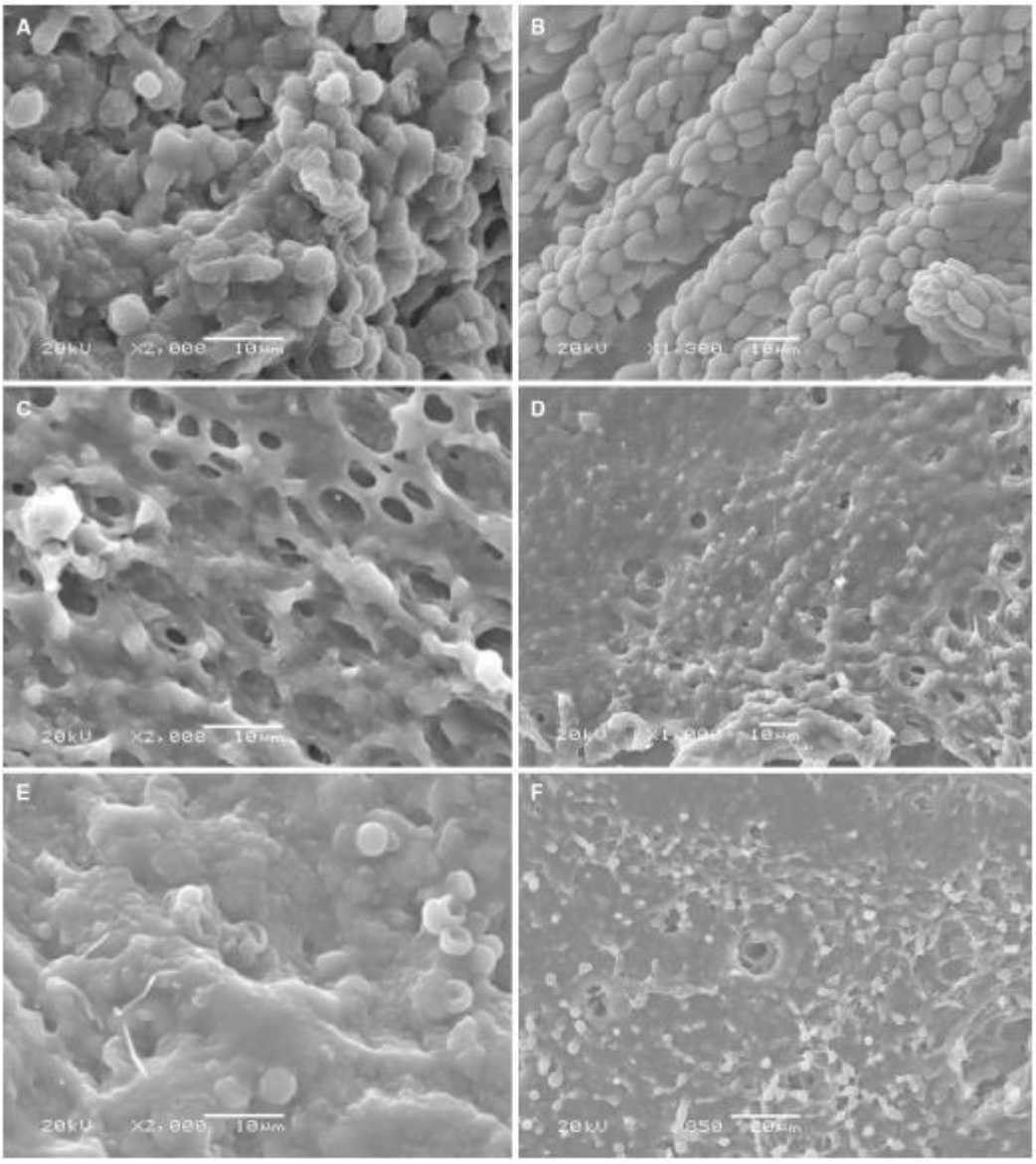


Figure 24: *Scanning electron microscope pictures of nasal mucosa :*
A and B: non exposed normal nasal mucosa
C: 24g OC during 5 minutes (1,28 damage score) *D: 24g OC during 10 minutes (2,00 damage score)*
E: 48g OC during 5 minutes (3,28 damage score) *F: 48g OC during 10 minutes minutes (3,71 damage score)*

On the respiratory system, capsaicin can cause pulmonary or tracheal edema [120]. Pre-existing respiratory conditions like asthma, acute bronchitis, or viral infections have increased sensitivity to cough reflex [121].

In a Randomized Controlled Trial (RCT), it was shown that, when OC spray was used from a distance of 5 feet in very good laboratory conditions, no significant differences were observed as for predicted forced vital capacity, percent predicted forced expiratory volume in one second, oxygen, or CO_2 levels [122].

A rare case of an 11-year-old boy who inhaled intentionally aerosol sprays involved one-hour coughing, before becoming asymptomatic and going to sleep. But four hours later, the patient developed stridor and respiratory distress, progressing to respiratory arrest and requesting intubation with pulmonary edema worsening during the 6 first hours after admission [123].

Respiratory failure and hypoxemia were observed in a 4-year-old child accidentally exposed to 5% OC gas. The treatment regimen included extracorporeal membrane oxygenation [124].

4) Cardiovascular system

Cardiovascular of Capsaicin are well documented [125-127]. Capsaicin induces complex effects on the cardiovascular system: tachypnea, hypotension (seen in the Bezold–Jarrish reflex), bradycardia, and apnea. The cardiorespiratory effects of capsaicin have been studied following intravenous dosing. Capsaicin treatment resulted in a triphasic effect on blood pressure and altered cardiac parameters [128, 129].

Fall in systemic blood pressure and reduction in the heart rate is caused by capsaicin sensitization of baroreceptors in the carotid sinus wall and in the pulmonary vessels [130, 131].

In dogs, capsaicin caused a sustained increase in the tension of spiral strips of proximal and distal renal arteries and distal mesenteric arteries [132].

In ex vivo experiments with whole heart preparations, capsaicin-perfusion caused a concentration-dependent increase in heart rate and calcitonin gene-related peptide (CGRP)-like immunoreactivity (LI) release in combination with a decrease in contractile tension [133].

The Kratschmer reflex, which causes cardiorespiratory dysfunction with apnea, bradycardia and a biphasic fall and rise in aortic blood pressure can be caused by capsaicin inhalation.

5) Thermoregulation

Thermoregulation is the mechanism by which an organism maintains a constant temperature. Thermoregulatory effects of Capsaicin and capsaicinoids have been described. Pretreatment or treatment of animals with capsaicin impairs thermoregulation irreversibly and severely affects heat escape behavior. Animals were unable to discriminate and seek cooler environments, consumed less water and became dehydrated. Heat stroke could not be prevented, with dermal blood vessels failing to dilate. Subcutaneous injections resulted in body temperature reduction. On human skin pretreatment with 1% capsaicin and capsaicinoids lowers the threshold to thermal pain [18, 27, 134-149].

6) Gastrointestinal tract

When capsaicin was given orally to human volunteers and caused burning sensation on the mouth, throat, chest and abdomen, and nausea, vomiting and diarrhea. The most common symptoms were oropharyngeal irritation and nausea [109, 150].

Capsaicin and capsaicinoids damage the duodenal epithelium and alter fat uptake [151-155]. Other studies showed that that capsaicinoids had no adverse effect on fat intake or absorption [152, 156, 157]. General absorption of nutrients and metabolism is affected [158]. It has been postulated that capsaicinoids counteract the accumulation of fat in the liver by the reduction of hepatic lipogenesis and/or increased oxidation of lipids [159].

7) Neural and neuroendocrine system

The neural system can be affected strongly by degeneration of neural fibers, more precisely by demyelination. This occurred in a 16-year-old boy exposed to pepper spray, who developed symptoms of a polyneuropathy close to those of Guillain-Barre syndrome [160].

Capsaicin also affects the neuroendocrine system [161].

8) Lethality

The probable lethal oral dose of capsaicin for humans is considered to be 0,5 to 5,0 g/kg [162].

In animal experimentation, OC produced from *Capsicum frutescenes var. Nagahari* and dispersed as a smoke was tested for inhalation Lethal Dose 50% (LD_{50}) in mice. It was found to be between 800 mg/kg body weight (at 8000 mg/m^3 dispersion for 20% capsaicinoids) to 283 mg/kg (at 7127 mg/m^3 for 40% or 5657 mg/m^3 for 80% capsaicinoids) [112].

30 deaths-in-custody following OC use have been reported in the early 1990s [163]. Strong effects were observed on the heart (Figure 25), but it could not be established if it was directly caused by OC exposure or a pre-existing condition. In another case, it was well established that OC caused death, with pulmonary edema and bronchitis (Figure 26).

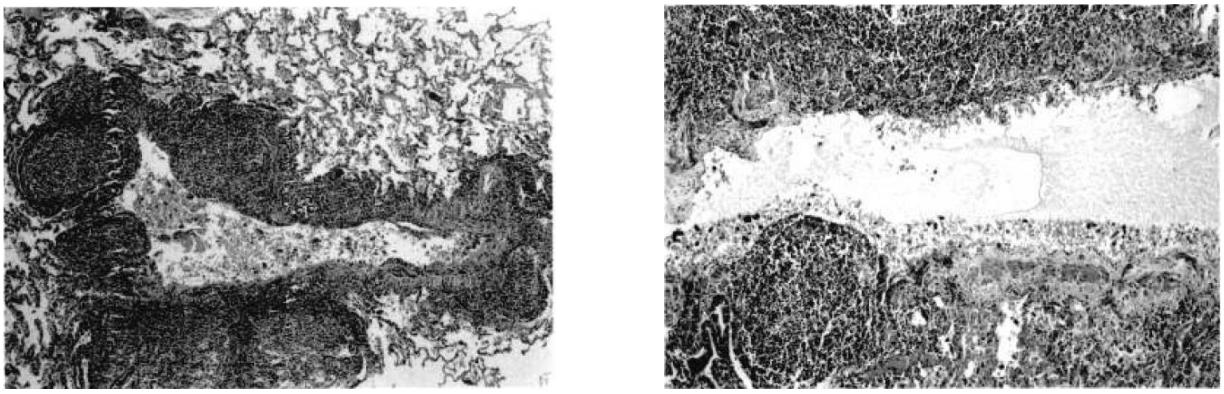


Figure 25: *Lung showing florid follicular bronchiolitis and bronchitis (left) and pulmonary*

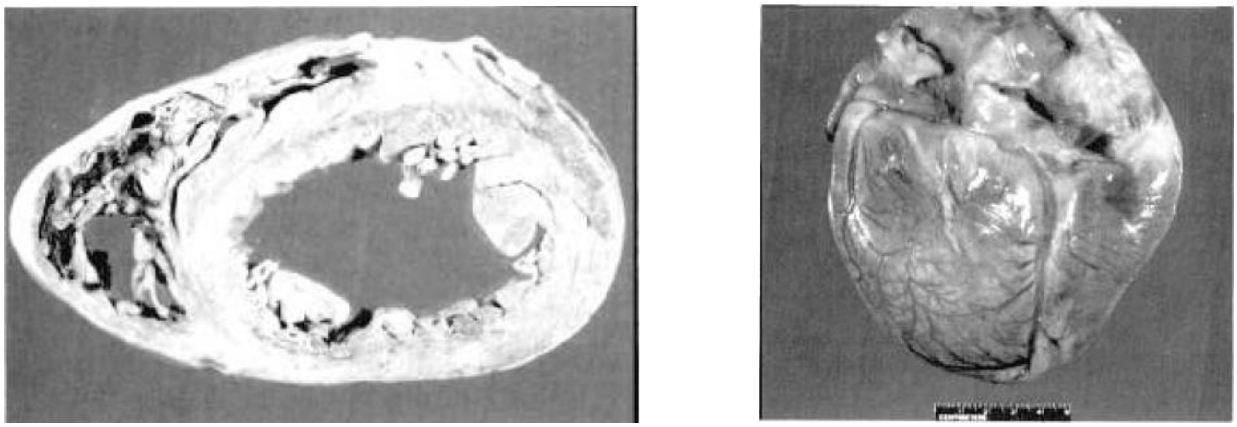


Figure 26: *Heart with remote infarct in the posterior left ventricle (cross section, left) and thinned wrinkled myocardium within the zone of remote infarct (posterior view, right)*

In general, it is very difficult to establish that riot control agents caused death from a forensic perspective. In some cases, OC could be determined as directly causing death, in others it was contributing to death either associated with excessive force or constraint, or because of pre-existing condition [164].

IV) Metabolism and cytotoxicity

Caspaicin influences multiple metabolic processes [165]. It is bio converted to electrophilic metabolites and other reactive moieties: ring epoxide, phenoxy radical and quinone (through hepatic cytochrome P-450-catalyzed conversion). These moieties can interact with nucleophilic sites of macromolecules such as proteins, DNA and RNA. This might be the reason for cytotoxicity, immunotoxicity, mutagenicity and carcinogenicity. In particular, quinone-mediated effects include alkylation of DNA and proteins (on cysteine residues), GSH depletion, reactive oxygen species (ROS) formation and ROS-related effects such as DNA oxidation and lipid peroxidation causing initiation, promotion and progression of carcinogenesis [166, 167].

Two metabolic pathways lead to quinone formation:

- O-demethylation of the 3-methoxy group on the vanillyl ring with concomitant oxidation to the semiquinone or o-quinone derivatives

- O-demethylation of the phenoxy radical intermediate of capsaicin, generating a methyl radical alkylating nucleic acids and proteins.

There are multiple effects caused by alkylation of proteins and GSH, affecting cellular energetics and detoxication processes, for instance through binding with microsomal protein with consequences on xenobiotic metabolizing enzymes and liver toxicity. Another way affecting the liver is through inhibiting hepatic mitochondrial bioenergetics by repressing NADH–quinone oxidoreductase activity [168].

Capsaicin metabolization is mainly hepatic [169], it was entirely metabolized in rat and human microsomes within 20 minutes [165]. In hepatic stellate cells, capsaicin inhibited dimethylnitrosamine-induced hepatic fibrosis by blocking the TGF-β1/Smad signaling pathway [170]. At high doses, capsaicin is associated with hepatotoxicity [171, 172].

TRPV1 independent effects of capsaicin involve other pathways like the direct inactivation of the microsomal prostaglandin E synthase-1/p38-mitogen activated protein kinase-MAPK-activated protein kinase 2-COX-2 (mPGES-1/p38-MAPKMK2-COX-2) pathway [173]. It has anti-inflammatory effects in the salivary glands as well, by inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [174]. It is used against gastric cancer which involves pit-oct-unc (POU) domain, class 3, transcription factor 2 (POU3F2) suppressed by capsaicin through tNOX downregulation, accompanied by apoptosis [175, 176].

V) Effectiveness

A review of 30 cases of death showed that the use of OC spray was often triggered after a struggle started, but was only considered as effective in four cases [177]. Other studies claim its effectiveness in reducing police officer's risks of being injured, although there is no real statistical significance in a 6-year study including 3 years of pre-OC and 3 years post-OC deployment. Questions that surround the use of OC agent are for governments according to their authors, "rather than clinicians" [4]. But health effects should be taken into account anyways in the balance towards decision-making. In the Netherlands, a study on OC usage by the Dutch Police Academy stated that "The solution to safe and responsible police interventions in potentially dangerous situations should not be sought one-sidedly in technology, but also in improving tactical and technical skills of police officers" [178].

Ballantyne suggested that statements about the 'safety-in-use' of OC sprays in civil disturbances should be made with thoughtful caution, since the evidence overall indicates that in a heterogeneous population there may be some serious adverse health sequelae [179]. Physician training and reduction in riot control agent concentration were also recommended [180]. Risks for law enforcement personal, especially because of long term health effects with repeated exposure also raised concerns [181]. Imminent violent threat or widespread violent acts in a protest that pose an imminent threat to public safety have not been reported in most situations where tear gas was used, thus urging to establish clear protocols of riot control agents use [182].

A study using data from police departments collected from 1998 to 2007 assessed the effect of non-lethal weapons on police officer safety and risk of injury on suspects. Despite decreasing injury risk in suspects, OC use did not reduce prevalence in officer injury, but actually increased it (Odds Ratio 1,42) [183].

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