TABLE 1. Clinical presentation and site exposure with oleoresin capsicum spray[4-18]

	Case series					
	Stopford,[6] 2004	Kearney et al,[4] 2014	Forrester and Stanley,[7] 2003		Watson et al,[5] 1996	Brown et al,[10] 2000
Study period (year)	1993-1995	2002-2011	1998-2002	2000-2002	1991-1994	1994-1996
No. of persons exposed	6000	3671	1531	762	908	100
Male / female	NR	1882 / 1722 (67 Unknown)	864 / 625 (42 Unknown)	NR	NR	87 / 13
Age range (mean) in years	NR	23-24	NR	NR	(27.6)	M: 17-56 (31.8) F: 19-54 (36.8)
OC concentration (%)	NR	NR	NR	NR	5	10
OC (SHU, million)	NR	NR	NR	NR	NR	NR
No. of persons requiring treatment	61 (1%)	NR	NR	NR	81 (9%)	NR
Symptoms, No. (%) of victims*						
Dermatological	5 (8†)	2183 (59.5‡)	821 (53.6‡)	NR	26 (32.1†)	NR
Burning sensation	NR	NR	NR	337 (44.2)	20 (24.7)	NR
Erythema	NR	NR	NR	125 (16.4)	12 (14.8)	NR
Erythema with blister	NR	44 (1.2)	NR	NR	NR	NR
Ocular	28 (46†)	1913 (52.1‡)	595 (38.9‡)	NR	63 (77.8†)	NR
Burning sensation	NR	NR	NR	290 (38.1)	45 (55.6)	NR
Lacrimation	NR	NR	NR	70 (9.2)	13 (16.0)	NR
Blepharospasm	NR	NR	NR	NR	NR	NR
Conjunctival injection	NR	NR	NR	90 (11.8)	36 (44.4)	38 (38.0)
Conjunctival proliferation	NR	NR	NR	NR	NR	NR
Corneal abrasion/erosion/ulcer	NR	134 (3.6)	NR	NR	7 (8.6)	7 (7.0)
Respiratory	20 (33†)	754 (20.5‡)	336 (21.9‡)	NR	6 (7.4†)	NR
Cough	NR	NR	NR	75 (9.8)	1 (1.2)	NR
Shortness of breath	NR	79 (2.1)	NR	NR	3 (3.7)	NR
Wheezing	NR	10 (0.3)	NR	NR	2 (2.5)	NR
Oral/throat irritation	NR	NR	NR	72 (9.4)	1 (1.2)	NR

Abbreviations: NR = not reported or not applicable; OC = oleoresin capsicum; SHU = Scoville heat units

* Total >100% as patients could have more than one exposure route and more than one clinical symptom

† The denominator was based on the number of victims requiring treatment

‡ The denominator was based on the number of victims exposed to pepper spray

hand-eye coordination. Victims are usually rapidly incapacitated although most symptoms resolve within 30 to 60 minutes. The use of pepper spray by the US police has been reported to be successful in subduing aggressive individuals in 90% of cases.[19]

Dermatological injury

Initial contact of capsaicin with skin or mucous membranes produces a violent irritation with subsequent desensitisation to irritant chemicals. Victims experience acute burning pain, tingling, erythema, oedema, and pruritus (the pain can be prolonged for several hours in persons not adequately decontaminated).[4,20] In prolonged exposure and in severe cases, persistent dermatitis with severe erythema and/or blister formation may occur.[4,20]

Kearney et al[4] made a retrospective chart review of all human exposures to pepper spray recorded in the electronic database of the California Poison Control System during 2002-2011 (Table 1). Of the 3671 victims recorded, the most common type of exposure was dermal (2183 victims, 59.5%) with 2080 (56.7%) victims reporting minor/self-limiting symptoms, and 103 (2.8%) reporting more severe symptoms that required medical evaluation, including persistent dermatitis, dermal burns, and/or blister formation.

Watson et al[5] conducted a retrospective study based on medical record review of 81 patients who presented to an emergency department after exposure to OC (908 individuals in total exposed during law enforcement) in 1991 to 1994 in Kansas City, Missouri, US. In 26 (32.1%) cases the chief symptoms upon arrival to casualty were pain or

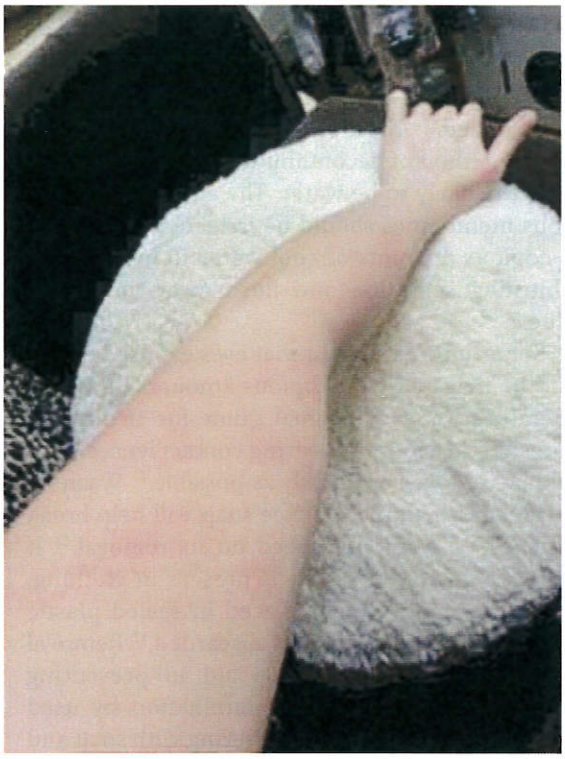

FIG 1. Dermatitis in the affected area 4 hours following exposure
(Reproduced with permission of Miss YY Tse)

Oleoresin capsicum spray can affect both morphology and sensitivity of the cornea. Brown et al[10] demonstrated that of 100 exposed individuals (10% OC spray), 7% (n=7) had corneal abrasion. Watson et al[5] found 8.6% (n=7) of 81 affected officers who required medical treatment actually had corneal abrasion. Epstein and Majmudar[23] described a case with keratopathy, and the victim's eye showed a corneal epithelial defect after OC spray to the eyes. Although the defects healed within 5 days of treatment with polymyxin-bacitracin ophthalmic ointment, smouldering inflammation persisted. Further treatment with tobramycin-dexamethasone drops every 4 hours caused the inflammation to subside but superficial stromal opacity remained, resulting in irregular astigmatism.[23]

Zollman et al[8] demonstrated that corneal sensation was severely affected after 10 minutes and 1 hour of exposure. At 1 week, sensation returned to baseline and corneal abnormalities disappeared. Apart from capsaicin, the carrier vehicle in which the active ingredient is dissolved may be toxic to corneal epithelial cells and cause temporary ocular irritation or superficial keratitis or erosion.[12]

Oral, nasal, and respiratory toxicity

Exposure may occur through inhalation, causing immediate inflammation of mucous membranes. Throat irritation results in a burning sensation, cough, choking, and inability to speak (due to laryngospasm or laryngeal paralysis). In the nasal mucosa, OC produces irritation, burning pain, sneezing, and a dose-dependent serous discharge.[24] Other respiratory symptoms have also been reported, including severe coughing, mucus secretion, shortness of breath, bronchoconstriction presenting as wheeze, and chest tightness. Direct contact of capsaicinoids with the vocal cords causes laryngospasm lasting 45 seconds.[21] Duration or magnitude of bronchoconstriction did not differ among normal subjects, smokers, and asthmatics.[21]

A review by Watson et al[5] of 81 victims of law enforcement action revealed that 7.4% (n=6) had respiratory symptoms after inhalation of OC spray, and 3.7% (n=3) complained of shortness of breath. Oh et al[13] studied an incident of OC gas leak in an urban shopping mall that affected 13 victims, of whom two (15%) experienced shortness of breath and eight (62%) complained of oral/throat irritation.

A controlled clinical trial involving 35 healthy subjects exposed to OC spray did not detect significant changes in predicted forced expiratory volume in 1 second (FEV_1) or oxygen saturation when compared with population norms.[25] The prone maximum restraint position reduced forced vital capacity (FVC) and FEV_1 by 15% compared with a sitting position, but there was no statistically significant difference in these parameters when use of OC and controls were compared in the restraint position.[25]

Systemic toxicity and death

Inhalation of OC spray can cause laryngeal and pulmonary oedema and chemical pneumonitis but this is rare.[21] An 11-year-old child who directly inhaled a jet spray from a pressurised container ultimately recovered but was reported to develop subglottic obstruction of the trachea and bilateral pulmonary infiltration that required intubation.[26] Billmire et al[27] described a 4-week-old healthy infant exposed to 5% OC when a self-defence device was accidentally discharged; the infant developed respiratory failure and hypoxaemia requiring extracorporeal membrane oxygenation. The patient was discharged and 12-month follow-up revealed several episodes of viral respiratory infections.[27]

Some studies have reported systemic symptoms including disorientation, fear, loss of body motor control (eg diminished hand-eye coordination),[28] hyperventilation, tachycardia, and pulmonary oedema.[21] The acute increase in blood pressure could cause headache, increased stroke risk and heart attack.[21] In a review of approximately 6000 (police) officers directly exposed to OC, eight (0.1%) trainees reported headache and chest problems that

shampoo, milk, or water), reported no significant difference in pain relief. Time after exposure appeared to be the best predictor for decrease in pain.[37] Medical treatment for dermatitis may include topical steroids, oral antihistamines, and topical antibiotics.

Discussion

Pepper sprays are generally regarded as immediately effective and less toxic than other riot-control agents such as chloroacetophenone (CN) and o-chlorobenzylidene malononitrile (CS). Both CN and CS are effective lacrimating agents with CN the most lethal. The estimated lethal dose (LCt_{50}) of CN, CS, and OC is 8500, 25 000 and >100 000 mg/min/m^3, respectively.[38]

Oleoresin capsicum spray contains the active ingredient capsaicin, which is obtained from chilli pepper. Typically, pepper spray weapons contain a 10% to 20% solution of OC. The capsaicinoid content determines the 'hotness' of preparation, commonly referred to as Scoville Heat Unit (SHU; Table 2). The scale is named after its creator, American pharmacist Wilbur Scoville. Sprays used in police work typically fall between 0.5 and 2 million SHUs.[8] The SHU governs the efficacy and pungency of pepper spray, thus the higher the SHU, the greater the inflammatory effect on skin and mucous membranes. A higher concentration of OC lengthens the necessary recovery period, thus affecting decontamination.[39] Greater than 5% OC might not atomise well into a fine spray (may clog the aerosol spray).[40] The capsaicin and related capsaicinoid content in most law enforcement OC sprays is between 1.3% and 2%. Areas of exposure can be dermatological, ocular, inhalational, ingestion or mixed, thus symptoms often involve more than one system. The prevalence of severe symptoms observed in various epidemiological studies varies from 2.7% to 15%.[4,5,7,10]

We found dermatological manifestation as the most common symptom in the case series (32%-100%),[5,8,11] although another study reported dermatological symptoms in only 8% of cadet officers exposed to OC.[6] The predominant site of exposure will be affected by any protective measures adopted: use of protective goggles or shields will greatly diminish exposure of skin to OC. Circumstances of OC spray use will also affect the predominant sites of exposure and severity of symptoms. Faced with confrontation during a public demonstration, officers will target OC spray at the eyes of protestors to quickly incapacitate them. This will result in a greater degree of both dermatological (face) and ocular exposure. Kearney et al[4] analysed the risk factors with the largest independent associations with more severe symptoms among 3671 cases exposed to direct OC spray designed to incapacitate during law enforcement crowd-control activities.

Multiple exposure of skin or mucous membranes over a period of seconds or minutes exaggerate the inflammatory response. Capsaicin exposure may diminish sensitivity to heat- or chemical-induced pain, and thus increase the risk and severity of dermal burns. Some authors have suggested that capsaicin can powerfully stimulate heat receptors to cause reflex sweating and vasodilatation, and activate hypothalamus-mediated cooling; this may result in an increased risk of hypothermia if victims are decontaminated with cold water on cold days.[41,42] Further, capsaicin-related cutaneous sensation may be heightened by perspiration, lacrimation, high humidity, and bathing at a warm temperature.[43]

The dermatological effects of capsaicin in OC spray have been further described in some case reports. 'Hunan hand' syndrome describes painful contact dermatitis in people preparing chilli peppers (containing capsaicin) by direct handling,[44] while Sweet's syndrome has been described following exposure to jalapeño peppers.[45]

Respiratory effects of OC spray involve cough reflex stimulation via capsaicin-sensitive nerves and bronchoconstriction. Although OC spray exposure causes cough and transient increase in airway resistance, experimental studies and clinical case reports show no evidence that patients with bronchial hypersensitivity are any more susceptible to the irritant effects of OC spray than those without.[5] No cases of occupational asthma due to capsaicin have been reported.[21] A cross-sectional study of workers exposed to capsaicin detected a statistically significant increase in complaints of cough in capsaicin-exposed workers, although there was no significant difference in FEV_1 and FVC between the two groups.[46] Not all asthmatics are sensitive to the bronchoconstrictive effects of OC spray.[21]

As capsaicinoids are lipophilic and have limited water solubility (16 μg/mL),[47] alcohols or other organic solvents are commonly used as a base to facilitate aerosolisation in pepper spray products. Suitable solvents include methylene chloride, isopropanol, propylene glycol, ethanol, and methanol. The solvent enhances capsaicinoid solubility to enable delivery to the intended target tissue. A gaseous propellant (usually nitrogen or carbon dioxide) is incorporated in the spray to discharge the canister contents.[1] Inhalation of high doses of some of these chemicals may produce adverse cardiac, respiratory, and neurological effects, including arrhythmia.[21] The health effects of solvent and propellants are beyond the scope of our study, but their potential hazards and effects need to be considered.

Little is known about the long-term effects of pepper spray. Concern has been raised about their mutagenic and carcinogenic effects considering

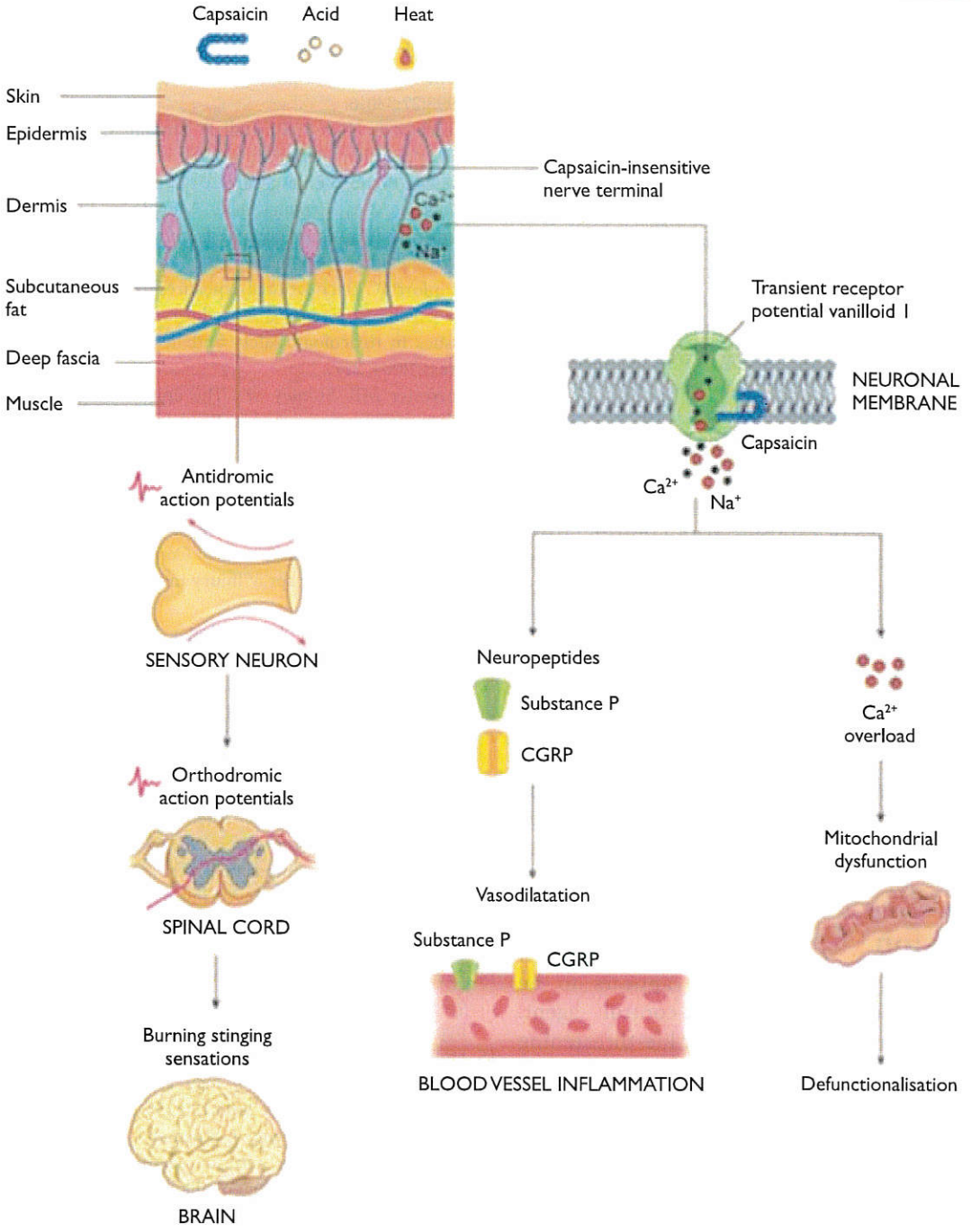

FIG 2. Schematic diagram of capsaicin-related cutaneous neurogenic inflammation
Skin is densely innervated by nociceptive nerve fibres for sensing stimuli in external environment. A large proportion of these afferent somatic nerves are fine polymodal unmyelinated C fibres or myelinated A delta fibres derived from dorsal root ganglia. Both respond to a range of physiological stimuli such as heat, cold, nociception, and mechanical distension. Upon stimulation by capsaicinoids, active neuropeptides are released resulting in an inflammatory response known as cutaneous neurogenic inflammation. This is characterised by transient burning pain, localised erythema, and circular oedema. In the final stage, a flared rim or edge appears around the circle with concomitant axon reflex vasodilatation. The axon reflex hypothesis of neurogenic inflammation suggests that damage to tissues triggers the immediate signal through the sensory nerves to the dorsal root ganglia and the central nervous system (orthodromic reflex), which transmits the sensation of pain. There is rapid depolarisation of the nociceptive terminals. The signal in the opposite direction, antidromic sensory nerve response induces release of vasodilatative neuropeptides (substance P and calcitonin gene-related peptides) in peripherally innervated tissues.[53]

The capsaicinoids contained within the pepper spray activate the TRPV1 receptor—the capsaicin receptor, a ligand-gated transmembrane calcium channel expressed at high levels by peripheral sensory nerves. These receptors are also expressed by keratinocytes (skin), tongue, and respiratory epithelium. Meanwhile, neurogenic inflammation in the airway blood vessels, epithelium, glands, and smooth muscles leads to vasodilatation, increased vascular permeability, neutrophil chemotaxis, mucus secretion, and bronchoconstriction.[21]
Abbreviations: Ca^{2+} = calcium ions; CGRP = calcitonin gene-related peptide; Na^{+} = sodium ions

22. Rasier R, Kukner AS, Sengul EA, Yalcin NG, Temizsoylu O, Bahcecioglu HO. The decrease in aqueous tear production associated with pepper spray. Curr Eye Res 2015;40:429-33.
23. Epstein RJ, Majmudar PA. Pepper spray in the eye. Ophthalmology 2001;108:1712-3.
24. Geppetti P, Fusco BM, Marabini S, Maggi CA, Fanciullacci M, Sicuteri F. Secretion, pain and sneezing induced by the application of capsaicin to the nasal mucosa in man. Br J Pharmacol 1988;93:509-14.
25. Chan TC, Vilke GM, Clausen J, et al. The effect of oleoresin capsicum "pepper" spray inhalation on respiratory function. J Forensic Sci 2002;47:299-304.
26. Winograd HL. Acute croup in an older child. An unusual toxic origin. Clin Pediatr (Phila) 1977;16:884-7.
27. Billmire DF, Vinocur C, Ginda M, et al. Pepper-spray–induced respiratory failure treated with extracorporeal membrane oxygenation. Pediatrics 1996;98:961-3.
28. Smith J, Greaves I. The use of chemical incapacitant sprays: a review. J Trauma 2002;52:595-600.
29. O'Halloran RL, Frank JG. Asphyxial death during prone restraint revisited: a report of 21 cases. Am J Forensic Med Pathol 2000;21:39-52.
30. USA: Excessive and lethal force? Amnesty International's concerns about deaths and ill-treatment involving police use of Tasers. Available from: http://www.amnestyusa.org/node/55449?page=72. Accessed 7 Dec 2014.
31. Steffee CH, Lantz PE, Flannagan LM, Thompson RL, Jason DR. Oleoresin capsicum (pepper) spray and "in-custody deaths." Am J Forensic Med Pathol 1995;16:185-92.
32. Granfield J, Onnen J, Petty CS. Pepper spray and in-custody deaths: international association of chiefs of police executive brief. RCMP Gazette 1994;56:12-7.
33. Pollanen MS, Chiasson DA, Cairns JT, Young JG. Unexpected death related to restraint for excited delirium: a retrospective study of deaths in police custody and in the community. CMAJ 1998;158:1603-7.
34. Lee DC, Ryan JR. Magnesium-aluminum hydroxide suspension for the treatment of dermal capsaicin exposures. Acad Emerg Med 2003;10:688-90.
35. Jones L, Tandberg D, Troutman WG. A controlled evaluation for household treatments for "chile burns". Vet Hum Toxicol 1986;28:486.
36. Vogl TP. Treatment of Hunan hand. N Engl J Med 1982;306:178.
37. Barry JD, Hennessy R, McManus JG Jr. A randomized controlled trial comparing treatment regimens for acute pain for topical oleoresin capsaicin (pepper spray) exposure in adult volunteers. Prehosp Emerg Care 2008;12:432-7.
38. Schep LJ, Slaughter RJ, McBride DI. Riot control agents: the tear gases CN, CS and OC—a medical review. J R Army Med Corps 2015;161:94-9.
39. Adkins LD. Oleoresin capsicum: an analysis of the implementation of pepper spray into the law enforcement use of force continuum in a selected police department. Available from: http://dc.etsu.edu/etd/779. Accessed 23 Jan 2015.
40. National Institute of Justice. Oleoresin capsicum: pepper spray as a force alternative. Available from: https://www.ncjrs.gov/pdffiles1/nij/grants/181655.pdf. Accessed 23 Jan 2015.
41. Tominack RL, Spyker DA. Capsicum and capsaicin—a review: case report of the use of hot peppers in child abuse. J Toxicol Clin Toxicol 1987;25:591-601.
42. Monsereenusorn Y, Kongsamut S, Pezalla PD. Capsaicin—a literature survey. Crit Rev Toxicol 1982;10:321-39.
43. Hilmas CJ, Poole MJ, Katos AM, Williams PT. Chapter 12: Riot control agents. In: Handbook of toxicology of chemical warfare agents. Available from: http://www.dtic.mil/dtic/tr/fulltext/u2/a539686.pdf. Accessed Oct 2015.
44. Weinberg RB. Hunan hand. N Engl J Med 1981;305:1020.
45. Greer JM, Rosen T, Tschen JA. Sweet's syndrome with an exogenous cause. Cutis 1993;51:112-4.
46. Blanc P, Liu D, Juarez C, Boushey HA. Cough in hot pepper workers. Chest 1991;99:27-32.
47. Kasting GB. Kinetics of finite dose absorption through skin 1. Vanillylnonanamide. J Pharm Sci 2001;90:202-12.
48. Durnford JM. Chapter 10: Genetic toxicity of riot control agents. In: Olajos EJ, Stopford W, editors. Riot control agents. Issues in toxicology, safety and health. New York: CRC Press; 2004: 183-200.
49. The American Civil Liberties Union of Southern California. Pepper spray update: more fatalities, more questions; 1995 Jun. Available from: https://www.aclusocal.org/issues/police-practices/pepper-spray/. Accessed 19 Nov 2014.
50. International Association of Chiefs of Police. Pepper spray evaluation project; 1995 Jun 22. Available from: http://www.theiacp.org/portals/0/pdfs/IntroPepperSpray.pdf. Accessed 19 Nov 2014.
51. Christensen RG, Frank DE. Preliminary investigation of oleoresin capsicum. National Institute of Justice Report 100-95, Gaithersburg, MD: National Institute of Standards and Technology; 1995.
52. Pershing LK, Corlett JL, Nelson JL. Comparison of dermatopharmacokinetic vs. clinical efficacy methods for bioequivalence assessment of miconazole nitrate vaginal cream, 2% in humans. Pharm Res 2002;19:270-7.
53. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816-24.
54. LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66:190-211.
55. Madsen CS, Johnsen B, Fuglsang-Frederiksen A, Jensen TS, Finnerup NB. Increased contact heat pain and shortened latencies of contact heat evoked potentials following capsaicin-induced heat hyperalgesia. Clin Neurophysiol 2012;123:1429-36.
56. Kennedy WR, Vanhove GF, Lu SP, et al. A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. J Pain 2010;11:579-87.
57. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth 2011;107:490-502.