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A Toxicological Review of Capsaicinoid
(Oleoresin of Capsicums)

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TECHNICAL REPORT

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SUMMARY

The extract (oleoresin) of the species *Capsicum* (peppers) has been formulated into a non-lethal weapon. Concern that its use could unintentionally induce toxicological effects, other than its enfeebling effect, prompted the Canadian Police Research Centre to seek a review. The literature research for toxicological effects was focused on acute exposure of the subject, that is, effects that can result following a short-term exposure to the skin, eye or respiratory system. Data has also been drawn from occupational and other settings where appropriate.

It is evident that exposure to small amounts of "Capsicum extracts" in an acute situation - as would be the case with the proposed use of the product - would not result in an obvious, irreversible toxicological outcome. However, systemically administered capsaicin, that is administered to the body as a whole, can be extremely painful. While these latter studies have been carried out under controlled laboratory conditions they provide little guidance as to what might happen in a "field" situation. **Of particular concern is the possibility of respiratory irritation and the effects this might have on clinically defined asthmatics.**

Overall, the hazard following acute exposure appears to be limited to the characteristic burning sensation expected of the capsaicinoids; it is a biochemical reaction that does not result lasting tissue damage.

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BACKGROUND

This review was prepared at the request of the Canadian Police Research Centre, which sought the assistance of the Environmental Health Directorate, Health Protection Branch, Health and Welfare Canada, in reviewing the human health aspects of the oleoresin of capsicum.

For centuries, the fruit of the genus *Capsicum* has been used as a condiment, either to flavour (chili, red, jalapeno, cayenne, etc., peppers), or to colour (paprika), otherwise bland foods (Maga, 1975). The active chemicals of *Capsicum* are not without their medicinal value as demonstrated in preparations such as Heet lotion, Infra-Rub ointment and Sloan's liniment (Locock, 1985). Although the first gustatory effects of capsicum were historically recorded by Chanca during Columbus' second voyage (Rumsfield and West, 1991), the current request deals with neither of those familiar uses but centres on a rather novel application for a food derivative; a formulated ingredient in a non-lethal weapon (SafStun, Cap-Stun).

This toxicological review will consider the active ingredients of *Capsicum*, specifically as formulated in the non-lethal weapon, and its possible health effects to an individual subsequent to acute exposure. It will present a brief literature survey of the toxicological effects on the human dermal, respiratory and ocular systems, followed by a summary of the expected hazards to an exposed individual.

A fuller account of the production, technology, chemistry and quality aspects of capsicum can be found in a five-part series written by V.S. Govindarajan (1985, 1986a, 1986b, 1987 and 1991).

INTRODUCTION

Capsaicin is the principal chemical of those essential oils called oleoresins which are characteristic of the genus *Capsicum* and is responsible for its pungency.

The amount of capsaicin contained in the *Capsicum* fruits and first isolated by E.K. Nelson in 1919 (Lee *et al.*, 1990) is said to range from about 0.1 to 1.0 % by weight (Monsereenusorn *et al.*, 1982, Rumsfield and West, 1991).

For almost a hundred years, it was thought that the active principle was a single substance (Maga, 1975) but capsaicin is now known to be a mixture of two unsaturated and three saturated homologs constituting the basic structure N-[4-hydroxy-3-methoxy benzyl]-alkyl amides (Govindarajan and Sathyanarayana, 1991). The mixture made up of 80 to 90% capsaicin and dihydrocapsaicin is more appropriately called capsaicinoids, that is, chemicals with a specific quality derived from *Capsicum*. Through this report capsaicin and capsaicinoids will be used as homologous terms.

PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of capsaicin (CAS registry number: 404-86-4) are; empirical formula = $C_{18}H_{27}O_3N$, molecular weight = 305.4 daltons, white crystalline platelets with a burning taste which has a threshold limit of approximately 10 ppm; is sparingly soluble in cold water but soluble in benzene, alcohol, ketone, ether, and paraffin oils (Monseerenuorn et al., 1982, Rumsfield and West, 1991). Govindarajan and Sathyanarayana (1991) reported that the capsaicinoids are the most intense pungent-stimulating compounds known. Those authors also reported that metabolic studies indicate that following consumption the capsaicinoids are not extremely stable in biological systems.

ACUTE ORAL TOXICITY

Acute toxicological parameters of capsaicin, selected for the purposes of this review, are reported as follows: oral LD, 60 - 190 mg/kg and dermal LD, > 512 mg/kg in mice (Glinsukon et al., 1980) and female rats, the acute oral LD, of a pepper sauce (Tabasco) was found to be 23.6 and 29.7 ml/kg body weight, respectively (Winek et al., 1982).

For comparative purposes, the normal diet in Thailand is said to include about 2.5 g of Capsicum per day which converts roughly to 0.5 to 1.0 mg of capsaicin per kg body weight (Rumsfield and West, 1991). Gosselin et al., (1984) gives Capsicum a toxicity rating of 3 which signifies a moderately toxic compound with a probable oral lethal dose of 0.5 - 5.0 g/kg for a 70 kg person.

DERMAL EFFECTS

Although the pharmacokinetics of percutaneous absorption of capsaicinoids are still unknown, the ensuing pain (neuralgia) resulting from exposure of the peripheral sensors of the skin (epidermis) to capsaicinoids is best described as a burning ache (dysesthesia). Scientific research has presented some understanding of the physiological transmission of the pain impulse.

In its simplest description, a chemical substance identified as simply "substance P", and which is structurally an undecapeptide (Rumsfield and West, 1991) is the principal transmitter of nociceptive (pain) impulses through specific peripheral sensory fibres to the central nervous system (Rumsfield and West, 1991).

According to a currently held hypothesis, topically applied capsaicin releases substance P, thereby, signalling pain. Also present at the site of capsaicinoid contact with the skin is a burning-stinging sensation and an erythema (redness) of the skin.

A consistent finding throughout the scientific literature is that Capsicum or the

extract of Capsicum when applied to the skin or buccal mucosa (i.e. the mouth) burns and causes pain with local desensitization (Collier and Fuller, 1984).

Concomitantly produced at the site of exposure is a long lasting desensitization to burning and pain. Repeated application continues to deplete substance P without blocking the sensations of touch, vibration and temperature. There may not be a block of sensation but there is an excessive sensitivity (hyperalgesia) or attenuation to heat and mechanical stimuli. The magnitude and duration of the effect are dose-dependent (Fitzgerald, 1983 and Simone ~~et al.~~ 1989). be noted that throughout all these studies it is a minuscule amount or volume that is being investigated.

A 1% solution of capsaicin in 85% ethanol induced a burning and stinging sensation to the skin which was hyperalgesic to heat for several days to weeks following application (Carpenter and Lynn, 1981).

Under experimental conditions which were designed to obtain a controlled stimuli and to overcome the diffusion barrier of the stratum corneum, Simone et al., (1989) discovered that 0.1 μg was the lowest amount of capsaicin to evoke pain when delivered intradermally in a 10.0 μl volume (i.e. 0.1% w/v). Depending upon the dose which ranged from 0.1 to 100 μg ., the pain could endure for either a couple of minutes or last for about 17 minutes.

If we contrast this to topical analgesic creams which produce "a comfortably warm feeling", the recommended application is no more than 3 or 4 times a day of a 0.025 to 0.25% concentration of capsaicin (Remington's Pharmaceutical Sciences, 1990). Repeated topical applications at low concentrations are said to induce long lasting desensitization to irritant chemical pain (Govindarajan and Sathyanarayana, 1991).

The unique physiological method of desensitization by capsaicinoids is being investigated in the hope that pain, in the future, can be more effectively controlled in patients. Desensitization caused by systemic administration can last for weeks or even months in the rat. Lee et al., (1991) also compared the structural-activity relationships of chemicals related to capsaicinoids in the rat and reported that analgesia against nociceptive pressure and its effects lasted - with intradermal injection - for ten days. If the statement holds true that experimental results on human skin can be corroborated in rat skin (Jancso et al., 1968), then, when considering dose-effect relationships, the desensitization effects of capsaicin sprayed on human subjects should last for a couple of days.

RESPIRATORY EFFECTS

Clearly given the proposed use of capsaicinoids, another physiological concern will be effects on the respiratory system. It is known that among pepper workers (Blanc et al., 1991) there was an occupationally related incident of cough. Furthermore, it is known

that cough and respiratory irritation can result from topical application of capsaicin (Hakas, 1990, Rumsfield and West, 1991). Although it was first reported that human bronchial tissue was affected by tachyphylaxis (a rapid immunization against the effect of toxic doses of an extract) under experimental *in vitro* conditions (Lundberg et al., 1983), an acute inhalation of capsaicin in human subjects challenged with repeated doses was observed to not induce tachyphylaxis (Choudry *et al.*, 1989).

Blanc *et al.*, (1991) measured three respiratory indices; prevalence of respiratory symptoms, alteration of lung function and an increase in the cough threshold, in order to determine the effect of capsaicin in workers who had been chronically exposed to hot chili peppers. The induction of cough in exposed workers through the inhalation of capsaicin ranged from 3×10^{-7} to 3×10^{-8} M (i.e. $\mu\text{g}/\text{ul}$). [The diluent was 1% ethanol in normal saline.] In comparison, strong bronchial contractions were measured in cultured bronchial tissue (*in vitro*) with 10^{-5} M of capsaicin (Lundberg et al., 1983). The bronchoconstrictor effect of capsaicin both *in vivo* and *in vitro* is mediated through substrate P.

Although it is known that capsaicin can elicit cough in man, Blanc *et al.*, (1991) concluded that it did not alter lung function nor did it appear to increase asthma or wheezing except in one subject. The exception was a non-asthmatic subject whose FEV₁ (forced expiratory volume) dropped by 24% while the asthmatic in the study did not respond any differently than the other subjects. The authors were unaware of any reported cases of occupationally induced asthma due to Capsicum.

It would appear that attempts to regulate coughing through respiratory flow rates may not be successful because Barros *et al.*, (1991) reported that "lower inspiratory flow rates were associated with a greater cough stimulus in the capsaicin challenge".

When it appears that the respiratory sensitivity of certain individuals has been aggravated because of cough induction by capsaicinoids, the noted coughing is more than likely to reflect an abnormality in the pathophysiology of the cough reflex, itself (Fuller, 1991). Fuller also reported that opiates inhibit capsaicin cough.

Inhalation of capsaicin (4 - 65 $\mu\text{mol}/\text{l}$; which may be expressed as 610 mg/l - 19.8 g/l) induced coughing in all 17 subjects with the number of coughs being dose dependent. The mild asthmatics of the study demonstrated no evidence of hypersensitivity. Furthermore, there was no evidence - it must be emphasized, under their experimental regimen (mild asthmatics, low doses) - of bronchoconstriction (Collier and Fuller, 1984). The effect of higher doses or low doses with more severe asthmatics has not been determined but it is possible that these situations could produce severe bronchoconstriction (Fuller, 1992, personal communication).

EFFECTS ON THE EYE

The literature is very sparse with respect to ophthalmological effects induced by capsaicinoids. Scarcity of clinical reports may reflect the transient nature of the Capsicum burn. Unlike burns caused by acids or bases the passing discomfort apparently does not permanently scar the cornea or sclera of the eye.

Instillation of capsaicin (50 $\mu\text{g/ml}$) into the eye of the rat evoked violent pain and blepharospasm (almost a complete closure of the eye) (Jansco et al., 1968). Winek *et al.*, (1982) could not distinguish whether the conjunctival irritation induced by the Tabasco sauce in the rabbit's eye was due to the vinegar or the capsaicin.

In her review on the relationship between capsaicin and neurosensory effects, Fitzgerald (1983) cited that a 1% solution of capsaicin in the eye of the rat did induce swollen mitochondria and a reduction in the number of microvesicles in nerve terminals but no cellular degeneration.

GENERAL

Although not central to the current discussion, a brief synopsis of general information relating to chronic and sub-chronic toxicity, that is, possible reproductive and carcinogenic effects as found in the literature is presented.

Centuries of culinary use as a condiment and the absence of epidemiological evidence of any adverse effects due to chili eating suggests that there are no cancer risks involved with capsaicin as a food additive (Govindarajan and Sathyanarayana, 1991).

Similarly, the absence in the literature of case reports, - especially from countries which indulge heavily in hot peppers - and the lack of any birth defects in the rat subsequent to oral gavage with capsaicinoids suggests an absence of teratogenesis (Winek *et al.*, 1982).

Intravenously administered capsaicin has induced a triad of effects in experimental animals; hypertension, bradycardia and apnoea (Szolcsanyi and Janossy, 1971; Govindarajan and Sathyanarayana, 1991). These specific circulatory and respiratory effects have not been discerned in human subjects following topical application or inhalation of capsaicin. Fitzgerald (1983) also concluded that systemically administered capsaicin can be extremely toxic.

The misuse or the abuse of any consumer product may prove to be fatal. Capsaicin is no exception. Winograde (1977) reported such a case of abuse, which almost proved fatal, when an "atypical croup" turned out to be a children's prank - of inhaling "deeply, several times, the jet of propelled substance" - of what was reported as either capsaicin, or an oil of cayenne, propelled by a fluorocarbon. There has been a

reported case of laryngospasm in an adult who accidentally inhaling several millilitres of a juice "liberally dosed" with tabasco sauce (Rubin et al., 1991).

SUMMARY

Every culinary enthusiast, at some time will experience, or will have experienced, after a spicy "hot" meal, the piquant palate pursued by dribbles of perspiration. Much less has been the uncomfortable burning experience of having picked or pickled "hot" peppers. What, however, will be the hazard of experiencing an acute exposure to a spray of capsaicinoids?

From the data, which could be gathered, it may be concluded that neither the acute oral toxicity, nor the acute dermal toxicity, nor the acute inhalation toxicity of capsaicinoids - under controlled experimental conditions - is evident in human beings. Such is not the situation with systemically administered capsaicin which can be extremely toxic (Fitzgerald, 1983).

The characteristically described "burning" of topically applied capsaicin is not toxicologically detrimental to tissue. Local application of capsaicin to a peripheral nerve is "never fatal" (Fitzgerald, 1983).

With regard to induction of allergies by capsaicinoids, they have not been reported in the literature. The adverse reactions to topical application can best described as a "burning, stinging, and erythema" (Rumsfield and West, 1991). Although the signs and symptoms may be descriptively similar to an allergic reaction, there is currently no known sensitization to capsaicin. Furthermore, the classical sensitization would be less likely because of the non-proteinaceous structure of the molecule.

Even though Capsicum has been rated as moderately toxic, 500 -5000 mg/kg, by Gosselin et al., (1984), the daily consumption rate as evidenced by people of Thailand, 1.0 mg/kg, suggests that human daily usage does not approach a toxic level. Furthermore, it can be noted that sodium chloride - ordinary table salt - has the same toxicity rating (Gosselin et al., 1984).

There is, fundamentally, a distinctly unique chemical characteristic of capsaicinoids which appears to discourage and even prevent attaining the level at which it would be toxic to human beings. That being, when one is exposed to the extract of Capsicum it causes the sensation of burning. The active ingredients of Capsicum are distinctly unique because the burn, unlike other chemical burns caused by acidic or basic solutions, or the agent, fire, does not induce necrosis. There appears to be no structural lesion to the treated tissue.

The work of Simone et al., (1989) demonstrates that in the absence of protective clothing for the human body the pain (i.e. burning) would begin at a concentration of

0.1% (w/v) capsaicin and last for a couple of minutes. increasing the dosages to 10 and 100 μg ., extended the pain to 9 and 17 minutes, respectively. The 10 and 100 μg of capsaicin were delivered intradermally in a 10 ul volume which can be converted to percentages of 50 and 90.

Other than pain, does acute inhalation of capsaicinoids, under field conditions, induce an intractable complication to an already stressed respiratory system - eg. asthmatics? From the data cited in this review there is no indication that capsaicinoids would induce some other acute epithelial or acute inhalation toxicity.

There is, however, an axiom in toxicology which states that the dose regulates the effect (The Bollingen Series, 1951). The dosages of capsaicin, as reported in the literature, were delivered in controlled small amounts to the lungs ($\mu\text{mole l}^{-1}$, Collier and Fuller, 1984) and were, overall, without adverse effects. What is lacking in the existing data is a dose-response curve from which one could extrapolate to maximum dosages likely to be encountered in actual use of the spray. Furthermore there are no reported field studies of the use of the capsaicin spray from which one might be able to estimate actual exposure and dose. Hence the hypothesis that inhalation of capsaicin by asthmatics is without effect needs to be tested in a properly designed protocol.

The chemical analysis of the formulated Capsicum products carried out by the Canadian Police Research Centre (1992) suggests that oleoresin concentration, depending on the units of expression, which can be either weight/volume or volume/volume of contents or the canister, may approximate a maximum of 10.0%. From the available data in the literature we have no way of knowing what the effects of spraying this concentration might be on an exposed individual or what the duration of pain might be.

There are too many unknown and confounding variables to allow for a completed assessment of hazard. For example, amount and duration of dose administered, a possible double exposure, state of epithelium (eg. perspiration, covering of dirt or oils), exposure to a less cornified area, and even the weather conditions (eg. rain, sunny, cold) at the time of exposure. Such factors will dictate how long the burning pain will persist. The controlled conditions of the laboratory are compromised in the field and it is not possible to extrapolate from controlled laboratory experimental data to the practical situation where the spray would be used.

What ever may be the site of exposure, skin, eye, or oral mucosa, there is one undisputable conclusion. There is the characteristically known burning pain of Capsicum.

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