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OC SPRAY – A REVIEW OF ITS POSSIBLE RISKS INCLUDING CARCINOGENICITY

By: Dr. Joseph Ruddick
Health Protection Branch
Product Safety Bureau

TECHNICAL MEMORANDUM

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NOTE: Further information about this report can be obtained by calling the CPRC information number (613) 998-6343

NOTA: Pour de plus ample renseignements veuillez communiquer avec le CCRP au (613) 998-6343

The following comments by Dr. Joseph Ruddick of the Product Safety Bureau, Health Protection Branch, were provided to the Canadian Police Research Centre (CPRC) as a result of some correspondence to the Centre which raised the issue of carcinogenic risks in the use of pepper spray.

The Canadian Police Research Centre is grateful to Dr. Ruddick for his considered reply to the concerns and to Dr. Ruddick and Health Protection Branch for their permission to print and distribute these comments for the information of the Candian police community.

Les observations suivantes du Dr Joseph Ruddick du Bureau de la sécurité des produits, de la Direction générale de la protection de la santé, ont été communiquées au Centre canadien de recherches policieres (CCRP) en reponse à la question parfois soulevée dans la correspondance adressée au Centre concernant les risques cancérogènes du gaz poivre.

Le Centre canadien de recherches policieres tient à remercier le Dr Ruddick de sa reponse aux preoccupations formulées et lui est reconnaissant ainsi qu'à la Direction générale de la protection de la santé d'avoir permis la diffusion de ces observations à la collectivité policière du Canada.

A Question of Carcinogenic Risk with Pepper Spray

I have appraised the memo written by Jeremy Brown, MD., with regard to the item dealing with an increase to the carcinogenic risk of "Capsicum Spray" because it is imputed, there, that "mutagenic data is sufficient that one time exposure could, conceivably, increase future cancer risk,'. Much of the legwork for this response was lightened by the receipt of the box of papers from the Canadian Police Research Centre holding the most recent publications on capsicum.

Cancer as a specific topic was very - very - briefly mentioned in the 1993 paper (Canadian Police Research Centre Annual Report, TR-02-03) which reviewed the acute toxicological aspects of capsaicinoid, because, as stated there, chemical carcinogenicity was "not central to the current discussion". It is unquestionably related to, at best, a chronic exposure. Chronic, or lifetime, exposure is a sharp contrast to the "acute" or "one time only" exposure which would be anticipated with the prescribed spray. Your request provides a welcomed opportunity to expand both upon the carcinogenicity issue and, at the same time, provide a response to your cancer risk querie.

The focal question is whether a human subject who is acutely' exposed to either a spray, or several sprays, of an oleoresin of the Capsicum species, will develop cancer as a result of the one-time exposure.

To classify the Capsicum family as carcinogenic requires that it complies with the toxicological standard. In other words, does the spraying (exposure) measure up to the scientific criteria set to determine carcinogenicity? My response to this question is taken from two composite areas of toxicology: toxicological principles and the inherent toxicity of the "hot" ingredient of peppers, capsaicinoid. The course that we are about to follow is common and it will fix the decision upon firm - tame and scientific - principles and not upon an untethered presumption. Furthermore, being aware that you will pass on our reply to others and, in addition, draw conclusions from it to resolve your interests, I therefore, want to provide you with a complete, but succinct, explanation.

Let us begin by first reiterating the toxicological criteria set down to determine a cancer-producing substance, that is, a chemical, such as, a medication, a food contaminant or an environmental agent as opposed to radiation. More often than not, the determination of carcinogenicity centres on an animal test that adheres to very basic, but fundamental, toxicological principles: principles that will direct us towards determining the possibility of cancer by a "spray of pepper".

'**Acute:** A relative term meaning an exposure which takes place for a very short time. It is set as within 24 hours [OECD, 1987. Guidelines for Testing Chemicals. Acute Oral Toxicity (No. 401)].

What gives scientists the confidence to state or report that a chemical is a carcinogen? The answer is that the chemical was subjected to scientifically acceptable tests and the toxicological evidence was validated, carefully evaluated and, then, established to be so. In other words, the diagnosis is cancer. And if we abide by the principles of toxicology, we know that during the assessment six well defined and characterized parameters were adhered to, without exchange or substitution of any one of them, in order to establish that the qualitative outcome of the treatment induced cancer in a laboratory mammal. The six are: I] chemical, 2] organism or biological tissue, 3] route of exposure, 4] amount (dose), 5] time (i.e. duration and frequency of exposure) and 6] an effected tissue or detrimental sign (see Methods in Testing for Carcinogenicity, p. 79-105, Principles and Methods of Toxicology, A. W. Hayes, 1982). These six parameters are the back bone - the sine qua non - of all toxicological tests (acute, teratological, 90-day, mutagenicity, etc.) which, as already stated, define toxicity within a specific and limited condition.

Rather than belabour the importance of each of the six parameters we will, for our purpose, "cut to the chase", which is '5] time'. The duration of all toxicological tests, in vivo, to establish carcinogenicity requires a chronic exposure. In the published "Testing for Carcinogenicity, Mutagenicity, Teratogenicity' (p. 19, Health and Welfare Canada, 1973) we read with regard to carcinogenicity testing that "... the material is administered daily over the life-span of the test animal..". Citing the World Health Organization (International Agency of Research on Cancer, Long-term and Short Term Screening Assays for Carcinogens; A Critical Appraisal, p. 37, 1980), "It is generally recommended that exposure of the test substance be started no later than a few weeks after weaning age and be continued for the major portion of the animals' lifespan." The same is asserted by the Organization of Economic Cooperation and Development (Guidelines for Testing Chemicals. Combined Chronic Toxicity/Carcinogenicity Studies; 1987) which also states that chronic exposure is the "... time which denotes the life span or at least half the animal's life span".

Therefore, according to the established protocol for carcinogenicity, the time required to chemically induce cancer in a mammalian test is chronic. Thus, if the capsaicinoids were to be carcinogenic in the human being, then their potency to induce any carcinoma, sarcoma, lymphoma or leukemia would only be revealed after exposing an individual to the correct dose, by the correct route and daily exposure for five days a week and unceasing for, at least, half the life time (i.e. 35 years for human beings). In short, it requires multiple - uninterrupted - exposures for a long period of time in order to cause the sought after tissue damage.

The concept that cancer can result from a single acute exposure was an inevitable assumption taken from the "one-hit" hypothesis which itself arose out of the radiation data, nonthreshold phenomenon, and the probability of single cell transformation. The

"one-hit" hypothesis implied that one molecule of a genotoxic carcinogen was sufficient to alter a cell's DNA such that the cell's natural physiology is turned towards cancer. Although still fostered by some scientists, it is not supported by the scientific evidence and the current understanding of the mechanism of carcinogenicity (see; Wilson J. D., Threshold for carcinogens: a review of relevant science and its implications for regulator policy. p. 3-36, 1997, in What Risk? Butterworth/Heinemann). Current knowledge of the molecular biology of cancer points to the importance of not only the dose load, but the duration and the frequency of exposure to a toxicant.

The next query, in our case, that is immediately raised, is what about the claim that the "mutagenicity data is sufficient that one time exposure could, conceivably, increase future cancer risk." The circumstances are opposite to that just mentioned (supra). Here, an acute exposure of cultured cells or microorganisms are used in a closed (i.e. cleidoic) system, with data generated from an in vitro test is thought to be indicative of carcinogenicity. Also, in order to subscribe to the hypothesis, credence must be given to intra species extrapolation for which the acute examination will have to be stretched from bacteria to human beings.

As a final contribution towards an understanding of the mutagenicity data, I cite the Health Protection Branch Genotoxicity Committee, which has written in its "Assessment of Mutagenicity"(p. 27)[2]: "Mutagenicity tests are tests for the induction of mutation and not tests for carcinogenicity".

As noted above, mammalian carcinogenicity is established within a very defined and restrictive condition which exists only when the six parameters (animal, dose, time, etc.) are preserved. We cannot change any of the parameters, that is, use different animals, different routes of administra-tion, different dosages, different exposures and different responses - and still ask for the same degree of credibility in the establishment of carcinogenicity. Something is logically and toxicologically wrong. Among other concessions, this claim would ask that carcinogenicity be a product of both acute and chronic exposure.

One of the fundamental principles in the assessment into the toxicological nature of a chemical, which holds the force of a law, is that you cannot extrapolate or form a judgement about its acute effects from the chronic situation, or vice versa. "Chronic toxic effects cannot be predicted from a knowledge of the effects produced by acute exposures..."(Ottoboni, M.A., 1991, The Dose Makes the Poison). Casarett and Doull (The Basic Science of Poison's, p. 14, 1991) also make the same point that "the toxic effects following a single exposure are quite different from those produced by repeated exposure". For example, one or two aspirins would do well to eliminate a headache

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[2] The Assessment of Mutagenicity, Health Protection Branch Mutagenicity Guidelines, Environ. Molec. Mutag. 21:15-37, 1993.

(acute), but to erroneously assume that a couple of aspirins a day would keep the headache away (chronic) would lead to stomach problems instead (i.e. gastritis).

Nevertheless, we are asked to have it both ways with Capsicum; that is, to have the chronic effect (cancer) reflected in the acute effect (mutagenesis). If we do not recognize the impossibility of this demand but are convinced that mutagenicity is synonymous with carcinogenicity then confusion would reign, and it does. A survey of the published scientific papers on this subject gives evidence that neglect of a toxicological principle, such as, a delineated distinction between acute and chronic, does generate confusion.

For example, in 1996, Surh and Lee published a minireview (Food Chem. Toxic, 34: 313-316) - following a short review (Life Sciences 56: 18451855) - entitled "Capsaicin in Hot Chili Pepper: Carcinogen, Co-carcinogen or Anticarcinogen?"- which postulates a possible mechanism to explain the dual nature of capsaicin. Contrary to these authors' desire, a chemical cannot both be a carcinogen and not be a carcinogen, or even prevent carcinogenicity, at the same time. While this may be possible within different species or at different dosages, it cannot be so within a fixed time. It may act as something other, such as a teratogen or show hepatotoxicity, but to be a carcinogen and not be a carcinogen at the same time defies the accumulated knowledge of toxicology. Induction of carcinogenicity is one of those very nebulous and obscure things in toxicology when you are trying to use one species (rat) to estimate the effect in another species (e.g. human beings).

Other papers convey the mutagenicity, dare we say 'carcinogenicity', conundrum of capsaicin which sometimes is weakly mutagenic for bacteria (Azizan and Blevins, Arch. Environ. Contam. Toxicol. 28, 284-258, 1995) and, at other times, when tested in the mouse, it is non-mutagenic (Muralidhara and Narashimhamurthy, Food Chem. Toxic.26:955-958, 1988). To compound the confusion, capsaicin may be a "potent mutagen" in Salmonella typhimurium following metabolic activation but not mutagenic in a mammalian test system (Nagabhushan and Bhide, Environ. Mutag. 7:881-888, 1985) however, the opposite is demonstrated with purified extracts of capsaicin (Gannett et al., J. Org. Chem. 53: 1064-1071, 1988) where the Ames assay, with or without activation, is "nonmutagenic" but the V79 mammalian cell assay is "mutagenic".

From a reading of the current published papers, the mutagenicity data for Capsicum extends to both ends of the spectrum as well as covers the shades in between. Anyone who cites its ability to foretell cancer has glossed over the confronting nature of acute and chronic toxicological effects as well as neglected to heed the caution sign. A caution that the mutagenic test as a confirmation of carcinogenicity must be weighed prudently because "40 % of rodent carcinogens . . . .are not detectable mutagens.. . .." (Ames, B. N. and L.S. Gold, J. Nat. Cancer Inst. Monogr. 12: 125-132, 1992).

Thus, capsaicin joins the category of another of those mysteries of science. Our worth as scientists will be measured on our understanding and ability to make the distinction by understanding the limit of each test.

Current experimental results for capsaicinoids, of both carcinogenesis and mutagenesis, are described as "discordant" (Park and Surh, Cancer Letters. 114: 183-l 84, 1997) and "limited" (Shlyankevich, M. et al., American Institute for Cancer Research, xiv, p. 212). To this should be added confounding and inadequate.

In the view of the foregoing, there is no conclusive evidence to support the contention that the Capsicum family induces carcinogenic effects in human beings under the conditions of an acute application as a spray. To state that it does, neglects both the fundamental principles of toxicology and the current science of Capsicum, as well as gloss over the limitations of mutagenicity tests. Furthermore, the evidence for the intrinsic carcinogenicity of the capsaicinoids is not evident, or demonstrably present at this time and, therefore, we can conclude that the statement in the letter to Dr. Brown should read ".... one time exposure cannot, conceivably, increase future cancer risk".

Joseph Ruddick
Health Protection Branch
Product Safety Bureau