COMMITTEE ON TOXICITY OF CHEMCIALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

STATEMENT ON COMBINED EXPOSURE TO 2-CHLOROBENZYLIDENE MALONITRILE (CS) AND PAVA (NONIVAMIDE) SPRAYS

COT/06/4 – January 2006

Introduction

1. The Committee has been asked by the Home Office Science Development Branch (HOSDB) for advice on the potential effects of exposure to both 2-chlorobenzylidene malonitrile (CS) and pelargonic acid vanillylamide (PAVA). CS and PAVA are dispersant incapacitant sprays used by routine patrol officers in police forces in England and Wales The HOSDB have reported that as the use of PAVA increases there is a clear possibility that use of both incapacitants on the same individual would occur. For example, cross border use by British Transport Police who use PAVA attending an incident in an area where the local police force uses CS spray. A further scenario would be use of one incapacitant in the field and a different incapacitant in the prison/detention cell area. There might also be operational reasons for use of more than one incapacitant in the field. However, the HOSDB has reported that individual officers would not be issued with more than one type of incapacitant. In addition, there is clear guidance that if officers found that a particular incapacitant does not work, there is no recourse to using a second type of incapacitant.[1,2]

CS (2-chlorobenzylidene)

2. CS is a peripheral sensory irritant[3]. It interacts locally with receptors on sensory nerves in the skin, eyes and other mucous membranes causing severe pain and irritation. Typical signs and symptoms during exposure include eye discomfort, excessive lacrimation, blepharospasm, burning sensation in the nose and throat, rhinorrhea, salivation, constricting sensation in exposed skin etc. The full effects arise within 20-30 seconds but some kind of effect is often seen immediately. Recovery is gradual and can begin within 15 minutes of being sprayed, with the disappearance of most effects within an hour later[1]. However, some individuals have taken up to 12-14 hours to recover completely. CS always has some effect even if not totally incapacitating. As CS affects the breathing as well as sight it tends to slow down and stop individuals much more quickly than PAVA, as they begin to panic when they think they cannot breathe. As CS affects a range of senses it can become disorientating. The HOSDB has reported that the short-term effects have led to the use of CS sprays by all but three police forces in England and Wales as a chemical incapacitant.[1] Such sprays consist of 5% CS in methyl isobutyl ketone (MIBK) with nitrogen as a propellant.[3]

PAVA (Nonivamide)

3. PAVA is a structural analogue of capsaicin, the active ingredient of natural pepper.[1] It is a potent sensory stimulant. It is also used as a food flavour (1 to 10 ppm in baked foods, meat products and soups; 57.9 to 93.1 ppm in chewing gum) and in human medicine (the rubifaciant, Nonivamide).

PAVA primarily affects the eyes causing closure and severe pain and this is its principal mode of action. The pain to the eyes is reported to be greater than that caused by CS.[1] The police guidance on the use of incapacitant sprays issued by the Association of Chief Police Officers advises that PAVA must enter the eyes for it to work effectively and the effects are normally instantaneous if this happens.[2] However, there have been occasions where there has been a delay between spraying and the effects taking place, or no effects at all. PAVA remains effective, with the eyes closed and extremely painful, for a longer time than CS before any recovery begins.[1] Once recovery starts, it is a rapid process[1] but people have been reported to be lacrimating for hours afterwards. Exposure to fresh moving air will normally result in a significant recovery from the effects within 15-20 minutes.[2] The pain worsens the first time the eyes are re-opened and then gradually subsides each subsequent time they are opened. PAVA spray consists of a 0.3% solution of PAVA in 50% aqueous ethanol with nitrogen as propellant

Trends in use

4. The HOSDB has reported that there are approximately 1500 CS discharges in England and Wales each year. PAVA spray is used by a number of forces including Sussex and Northamptonshire police forces. There are no data available on the number of PAVA discharges per year. There are a number of police forces who are in the process of considering a change to or adoption of PAVA. The HOSDB have reported that to date there is no information to suggest that both CS and PAVA had been used on the same individual, but as the use of PAVA increases there is a clear possibility that use of both incapacitants on the same individual would occur. The decision of when to use an incapacitant spray is left to the judgement of individual officers using the Officer Safety Model.[1,2]

Overview of previous COT consideration of CS and PAVA

5. The COT published statements reviewing the toxicity data on CS in 1999[3] and on PAVA in 2002[4] and 2004[5]. The overall conclusions reached on CS and PAVA are reproduced below

CS

6. In May 1999 a statement was issued by the Committees on Toxicity (COT), Mutagenicity (COM) and Carcinogenicity of Chemicals (COC) in Food, Consumer Products and the Environment regarding the use of CS spray as a chemical incapacitant. A copy of the full statement can be found at http://archive.food.gov.uk/dept_health/archive/cot/csgas.htm

i. The Committee noted that there are considerable data available to assess the toxicity of CS itself, and to a lesser extent, the solvent MIBK itself. CS is a potent sensory irritant, particularly to the skin and eyes. It is rapidly hydrolysed and therefore tissue exposure to CS itself is transient. Experience of use indicates that it is a skin irritant and thee are some reports of skin sensitisation occurring.

ii. There are no concerns relating to the mutagenicity, carcinogenicity or teratogenicity of CS itself.

iii. The toxicity of the solvent MIBK used in the spray is characterised by the transient local effects and central nervous system effects, particularly headache and nausea, resulting from exposures of about 100 ppm and above of teratogenicity in developmental toxicity studies. There is no information from carcinogenicity or multigeneration reproductive toxicity studies.

iv. Little toxicological information was available on the formulated spray. A 7% (w/v) solution of CS in MIBK produced severe irritant effects in rabbit eyes followed by recovery in 8 days. The spray has skin irritant properties and can cause dermatitis.

v. The Committee had concerns regarding exposure to CS spray in susceptible groups. Individuals with asthma or chronic pulmonary obstructive disease whose condition could be aggravated by the irritant effects of CS spray on the respiratory tract. Individuals with hypertension or other cardiovascular disease whose condition may be affected by the transient effects of CS spray in increasing blood pressure. It was not possible, on the basis of the available data, to comment on whether individuals being treated with neuroleptic drugs are more likely to be sensitive to the effects of CS spray.

vi. The Committee noted that adherence to the operational guidelines for the use of CS spray was of particular importance since at the time of exposure it would be exceedingly unlikely that the medical status of those exposed would be known. It was concluded that particular care needs to be taken to follow the recommended aftercare guidelines for all persons exposed to CS.

vii. The Committee considered that further information needs to be obtained on the effects of CS spray in humans. In this regard, it was noted that systematic studies in volunteers to investigate the toxicity of CS spray may present insurmountable difficulties. The Committee recommended that follow-up studies be carried out on people treated for the immediate effects of CS spray to obtain data on whether delayed effects occur. It was recommended that information should also be collected in these studies relating to the previous medical history of the individuals involved, particularly with regard to respiratory or cardiovascular disease, or treatment with neuroleptic drugs.

PAVA

7. The full COT statements from the evaluations undertaken in 2002 and 2002 can be found at http://www.advisorybodies.doh.gov.uk/cotnonfood/pava.htm and http://www.advisorybodies.doh.gov.uk/cotnonfood/pava04.htm . The overall conclusions are reproduced below.

i. The COT recognised that exposures would be low and for a short period. The Committee stated that it was impossible to calculate exposure with any accuracy but noted that dermal exposure would be of the order of 30 mg PAVA from a one second burst, with about 3 mg being absorbed. Any systemic exposure is likely to be of the order of 0.04 mg/kg bw.

ii. Animal model data and experience in use do not give rise to concerns regarding long-term harm to the skin and eyes arising from irritant effects. No conclusions can be drawn from the one available animal study to investigate skin sensitisation but experience in use, including in human medicines for topical application, indicates that PAVA is not a skin sensitising agent.

iii. There are no concerns regarding the mutagenicity of PAVA. PAVA gave a positive result in one of the three in-vitro mutagenicity tests carried out indicating that it could have mutagenic potential and negative results from an unscheduled DNA synthesis study and a bone marrow micronucleus test.

iv. There are no concerns regarding developmental toxicity. PAVA had low toxicity by the oral route, with no significant effects being seen in the maternal animals at doses up to 1000 mg/kg/day. The only effect seen in the developing offspring at this dose level was a small reduction in fetal weight. There was no evidence of any malformations, skeletal anomalies, or any other adverse effects at this dose level. The NOAEL for effects on the offspring was 500 mg/kg/day, about 4 orders of magnitude above the expected exposure level arising form the use of the spray.

v. The data from inhalation studies in volunteers, including those with mild asthma, indicate that there are unlikely to be any adverse respiratory effects in healthy individuals. It is possible that respiratory effects may occur in asthmatics, particularly since effects were observed in asthmatic volunteers at 0.1% PAVA, which is lower than the 0.3% used in the spray, and given the increased stress likely when the spray is used.

vi. The available information, both from the toxicity data in experimental studies and experience in use, indicates that the low exposures arising from the use of PAVA incapacitant spray would not be expected to be associated with any significant adverse health effects. The Committee recommended continuation of the monitoring of experience-in-use.

CS/PAVA Sprays – Potential Interaction

8. The COT approach to the consideration of combined toxicological action of a mixture of CS and PAVA is based on the concepts described in the COT Report on Risk Assessment of Mixtures of Pesticides and Similar Substances.[6] A key aspect of the approach to the assessment of the combined risk involves consideration of the mode-of action of critical toxicological effects. Table 1 (appended at the end of this statement)

summarises the potential interaction between CS and PAVA. The most evident area for potential interaction relates to effects at the site of contact, e.g. skin, eyes and respiratory tract. Some more detailed information on potential site of contact effects and their modes of action is given below.

CS Spray – Site of Contact Effects

9. CS is an SN_2 alkylating agent and reacts readily with nucleophilic sites.[7,8] Prime targets at the site of action include sulphydryl-containing enzymes such as lactic dehydrogenase. The findings of Cucinell et al suggest that lactic dehydrogenase is inhibited by CS, which was partially reversed by the addition of excess glutathione. Based on these results it has been suggested that alkylation of nucleophilic sites, including SH containing enzymes, is the underlying biochemical lesion responsible for CS-induced toxicity. CS reacts rapidly with the thiol groups of dihydrolipoic acid, the disulphydryl form of lipoic acid which is a coenzyme in the pyruvate decarboxylase system.[9] Alteration in dihydrolipoic acid biochemistry can lead to decreased acetyl CoA levels, resulting in cellular injury. CS has the ability to generate bradykinin *in-vitro*[10] and *in-vivo* in humans[7] and it has been suggested that the irritant and painful effect of CS may be due to bradykinin release.[9]

10. A recent report details a number of instances in which six police officers and a doorman developed a range of unpredictable long-term cutaneous reactions following both single and multiple exposures to CS spray over several months or years.[11] The six cases detailed in the report are out of out of the estimated several thousand officers who have used CS spray operationally over the last decade. The skin reactions consisted of contact allergy, leukoderma, initiation or exacerbation of seborrhoeic dermatitis and aggravation of rosacea. The skin reactions required long-term changes in working practice for the exposed individuals

PAVA Spray – Site of Contact Effects

11. Nonivamide, or synthetic capsaicin, has long been used as a topical application for the treatment of painful conditions of the muscles, joints and bones. Repeated or prolonged topical application of low concentrations or systemic administration of a single high dose can cause long lasting selective desensitisation.[12] Nonivamide binds to membrane receptors and selectively interacts with polymodal nociceptive neurones .[13] After binding, the membrane depolarises subsequent to the opening of a cation non-selective ion channel. As a result, the neurotransmitter substance P and other neurotransmitters are released from the nerve endings causing a sensation of burning pain and hyperalgesia. Prolonged and repeated administration of nonivamide causes desensitisation and inactivation of the sensory neurones to thermal, chemical and mechanical stimuli in a dose-dependent manner. Systemic nonivamide produces antinociception by binding to vanilloid receptors on afferent nerve endings in the spinal cord. Prolonged inactivation of sensory neurotransmitter release blocks spinal neurotransmission.

Studies of co-exposure to CS and PAVA

12. There are no studies of co-exposure to CS and PAVA. However, Foster and Weston (1986)[14] used a blister base testing approach in volunteers to assess pain response for CS and PAVA. They reported that PAVA induced more pain than CS. An inflammatory flare was often also noted with PAVA. The study of interaction used a desensitising protocol followed by a challenge by a different sensory irritant. The authors reported that when PAVA was used first it provided a generic desensitisation to challenge by other sensory irritants. When CS was used in the desensitising protocol there was a pain response from a subsequent PAVA challenge equivalent to that seen in control exposures.[14]

COT consideration of potential interaction between CS and PAVA.

13. Members were aware that concerns had been raised regarding possible sensitive subpopulations following exposure to incapacitants during the previous considerations of CS and PAVA. There was some evidence from volunteer trials that PAVA may exacerbate bronchospasm in asthmatics.[4,5] However no equivalent studies in asthmatic volunteers exposed to CS were available. The COT had noted in 1999 that CS might aggravate bronchial asthma in some individuals. There was thus some uncertainty regarding the potential effects of co-exposure in this subpopulation.

14. Members considered potential interaction between CS and PAVA might occur in relation to site of contact effects. The only available study where co-exposure had occurred related to a desensitisation protocol using a human skin blister base approach.[14] There was evidence that desensitisation with PAVA gave rise to no pain response upon challenge with CS. However desensitisation with CS did not have any effect on the pain response to PAVA. Overall members felt that the potential effects of co-exposure or sequential exposure to CS and PAVA would give rise to at most an additive effect, although there was a possibility that desensitisation to contact effects might occur.

15. The committee was aware that there had been a request for follow-up of individuals sprayed with CS, but no data had been forthcoming in view of the lack of compliance by individuals sprayed with CS with requests for clinical follow-up. The Committee explored possibilities for investigating possible adverse interactions. One suggestion was that it might be possible to review a summary of data from custody records for relevant information on effects in individuals who had been sprayed with CS and/or PAVA. Members suggested that police forces should flag all incidents where a police surgeon had been called to attend an incident or police station and that a summary of the number of such incidents (relating to CS or PAVA or combined exposure) should be made available. If possible information on whether individuals experienced breathing difficulties should be recorded**.** The Committee also noted the evidence from case reports of allergic sensitisation in police officers exposed to CS for a possible enhancement of skin effects in individuals with rosacea. Although the available evidence came from only a few individuals, in the context of the number of officers exposed or who have used CS sprays, it was felt that further surveillance for potential skin sensitisation among police officers was needed.

COT conclusions

16. Co-exposure to CS and PAVA is likely to result in, at most, additive effects on skin, eyes and respiratory tract in most individuals, although in some individuals a lower response might occur as a result of desensitisation.

17. The COT recommended that police forces should flag all incidents where a police surgeon had been called to attend an incident or police station and that a summary of the number of such incidents (relating to CS or PAVA or combined exposure) should be made available, together with any available on whether exposed individuals experienced breathing difficulties.

18. The COT agreed that the Association of Chief Police Officers (ACPO) should be asked to consider surveillance for potential skin sensitisation among police officers.

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TABLE 1. SUMMARY OF POTENTIAL FOR TOXICOLOGICAL INTERACTION OF CS AND PAVA

Toxicological end point	MIBK	CS	PAVA (50% in ethanol)	Potential for interaction
Metabolism	Metabolised & cleared predominantly as metabolites (enzyme inducer)	Rapid in seconds	Some absorption across skin in 50% ethanol. Extensive hydrolysis in liver/skin	Unlikely following single co-exposure
Acute Toxicity (systemic effects)	Low acute toxicity	Low acute toxicity	Moderate acute oral (Capsaicin)	Unlikely following single co-exposure
Skin Irritancy	Low skin irritancy (defattening)	Sensory irritating with prompt recovery. Mild skin irritant	Mild skin irritant up to 3 days in rabbit	Potential for interaction at sensory receptors possible. Effects might be altered by solvents.
Eye Irritancy	Low eye irritancy	Severe eye irritant in MIBK (effects dependent on solvent)	Significant eye irritant (reversible)	Potential for increased severity of effect likely.
Skin sensitivity	No evidence from available studies.	Evidence from human exposure of skin sensitivity	LLN assay considered inadequate. No evidence of skin sensitisation from medicinal use	Unlikely following single co-exposure
Mutagenicity	No evidence of mutagenicity from available studies	*In-vitro* mutagen and aneugen. Negative *in-vivo* mutagen	Positive evidence from an *in-vitro* chromosome aberration assay. Negative in two *in-vivo* mutagenicity assays.	Unlikely following single co-exposure
Carcinogenicity	No data available	No evidence of carcinogenicity including sites of contact (these data were used to assist the mutagenicity evaluation)	No data available.	Unlikely following single co-exposure
Repeat dose systemic target organs	Liver, kidney (rat)	None identified	None identified	Unlikely following single co-exposure
Reproduction	No evidence of adverse effects	No study available	No study available	Unlikely following single co-exposure, but no data on PAVA available.
Teratogenicity	No evidence of teratogenicity	No evidence of teratogenicity	No study available	Unlikely following single co-exposure, but no data on PAVA available
Human data	Localised irritation and CNS depression at >100 ppm. Odour threshold 0.4 ppm, irritancy threshold 2 ppm	0.5-1mg/m^3 involuntary closure of eyes (blepharospasm), burning in mouth, nasal irritation, tightness in chest. Skin irritation, contact sensitisation reported. Sever pain in contact with eyes	Application in accordance with specified use resulted in bronchospasm in some asthmatics.	Potential for interaction of local site effects on eyes, skin and respiratory system.

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