COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON THE USE OF PAVA (NONIVAMIDE) AS AN INCAPACITANT SPRAY

Introduction

1. In 2001 the Home Office requested advice from COT on the health effects arising from the use of a chemical incapacitant spray containing pelargonyl vanillylamide (PAVA or Nonivamide). PAVA is the synthetic equivalent of capsaicin the active ingredient of natural pepper. It is a potent sensory stimulant. It is also used both as a food flavour (at up to 10 ppm in the diet) and in human medicine (topical application as a rubifacient). In the USA it has been given GRAS (Generally Regarded as Safe) status by the FDA as a food flavour.

2. The Sussex Police Force have now been using PAVA spray since 2001, following a pilot exercise in 2000. It is now being used by 2 other police forces in the UK, as well as by police forces in other European Countries and in North America.

3. The COT considered this use in 2001 and agreed a statement in April 2002, which incorporated the advice of the COM on the available mutagenicity data. This gives details of the structure of PAVA, its use and a summary of the available toxicity data at that time.

4. The following conclusions were reached:

(i) We consider that it is not possible to make a complete assessment of the likely adverse health effects that could arise from the use of PAVA spray as a chemical incapacitant in view of the limited data available.

(ii) We recognise that exposures would be low and for a short period. It is impossible to calculate exposure with any accuracy but we note that dermal exposure would be of the order of 30 mg PAVA from a 1 second burst, with about 3 mg being absorbed. Any systemic exposure is likely to be low (of the order of 0.04 mg/kg bw).

(iii) The animal model data and experience in use do not give rise to any concerns regarding long term harm to the skin or eyes. However consideration needs to be given as to whether those wearing contact lenses might experience increased irritant effects. It is also noted that

no data are available on the potential of PAVA to induce skin sensitisation.

(iv) The *in-vitro* mutagenicity data, and consideration of metabolites, indicate that PAVA has some mutagenic potential; although negative results were obtained in an *in-vivo* study to investigate mutagenic effects in the bone marrow, data from a further study are needed to provide adequate assurance that this activity cannot be expressed *in vivo*. An *in-vivo* study to investigate the induction of unscheduled DNA synthesis (UDS) in the liver would be appropriate in this regard.

(v) No data are available to assess whether PAVA has any effects on the reproductive system. In particular the lack of any developmental toxicity studies is of concern as it is possible that pregnant women may be exposed to the spray.

(vi) The data from inhalation studies in volunteers, including those with mild asthma, indicate that there are unlikely to be any adverse respiratory reactions in normal individuals. Some respiratory effects may well 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 conditions of increased stress likely when the spray is used.

(vii) Further monitoring of experience in use, including the police officers using the spray, is recommended with particular consideration being given to eye irritancy in those wearing contact lenses and to effects in those with asthma or hay fever and in women who may be pregnant.

New data

5. In response to the conclusions in the COT statement Sussex Police have commissioned further studies to provide information on the data gaps highlighted. These comprise a further *in-vivo* mutagenicity study (the liver UDS assay) [1] , an investigation of skin sensitisation potential using the local lymph nose assay [2], and an investigation of effects on reproduction using a developmental toxicity study [3,4]. In addition they have provided some information on experience in use since the COT last considered the issue [5-8]. PAVA is now being used as an incapacitant spray by 3 Police Forces in the UK.

6. The COM considered the new *in-vivo* mutagenicity data at their meeting on 5th February 2004. They concluded that the in-vivo liver UDS assay was done to the current OECD guideline (N° 486) and was adequate. There was no evidence for the induction of DNA repair, as measured by unscheduled DNA synthesis, in the assay. The COM concluded that the information sought by the Committee had now been provided and that it was

possible to conclude that PAVA would not be expected to be an *in-vivo* mutagen [9]. No further mutagenicity data were required.

7. The COT considered the new data on skin sensitisation, reproductive toxicity and experience in use at their meeting in May 2004.

8. The ability of PAVA to induce skin sensitisation has been investigated in mice using the local lymph node assay [2]. The methodology was consistent with that given in the OECD guideline N° 429. Dose levels of 0.8, 2.1 and 4.1% PAVA were employed. Negative results were reported. However there was a high level of inter-animal variability, with for example, very low individual scintillation counts in 2/5 animals treated at the highest dose level. In addition it was felt that a concurrent positive control should have been carried out, as the laboratory concerned appeared to be relatively inexperienced in this assay. No conclusions could therefore be drawn from this study.

9. The potential of PAVA to induce adverse effects on development following exposure *in-utero* has been investigated in the rat in a study that conformed to OECD test guideline No. 414, with oral dosing (gavage). Dose levels used in the main study were selected following a preliminary developmental toxicity study in which no effects were seen on embryo-fetal development at doses up to 1000 mg/kg (the maximum dose level recommended in the OECD guideline 414) [3]. In the main study animals were dosed at 100, 500 and 1000mg/kg on day 5-19 of gestation [4]. They were then killed and their uteri and contents examined in the usual way. The only significant effect seen was a slight but statistically significant, reduction in fetal weight at the top dose level. The no observed adverse effect level (NOAEL) was 500mg/kg. This was not of concern in view of the large margin of safety.

10. Further data provided by Sussex Police did not indicate any significant adverse effects arising from the use of this spray either in the general public or in officers using the spray [5]. Experience in use has not identified any groups that are particularly sensitive to the spray.

11. Regarding the COT conclusions in 2002, the only outstanding data related to skin sensitisation, in view of the inability to draw any conclusions from the local lymph node assay on mice. As an alternative to repeating this study, consideration was given to obtaining information on the experience in use of PAVA as a topical medicine. As noted earlier it is used, at up to 0.4%, in topical medicines, sometimes under occlusion. Information on whether there was any history of skin sensitisation arising from such use was considered by the Committee at their September 2004 meeting. Data provided by industry and also by the Medicines Healthcare products Regulatory Agency (MHRA) were considered [6-8]. Products containing up to 0.4% PAVA have been used in human medicines for topical application in many countries, including the UK, for over 50 years. They are generally well tolerated with an insignificant number of adverse reactions. In the UK there have been reports of only 2 adverse reactions (both involving a rash) over the

last years. It can be concluded that PAVA does not have any significant skin sensitisation potential in practice.

Revised conclusions

12. Following consideration of these new data the COT agreed the following revised conclusions on the health effects of the use of PAVA incapacitant spray

(i) We recognise that exposures would be low and for a short period. It is impossible to calculate exposure with any accuracy, but we note that dermal exposure would be of the order of 30 mg PAVA from a one second burst, with about 3mg being absorbed. Any systemic exposure is likely to be low (of the order of 0.04 mg/kg bw).

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

(iii) The new in-vivo mutagenicity data provided (negative results in an *in-vivo* liver UDS assay conducted to internationally accepted guidelines) in conjunction with previously evaluated studies allow the conclusion to be drawn that PAVA is not an *in-vivo* mutagen.

(iv) The ability of PAVA to induce adverse effects on the developing offspring following *in-utero* exposure has been investigated in a prenatal developmental toxicity study in the rat using oral exposure (by gavage). The compound had low toxicity by the oral route, with no significant effects being seen in the maternal animals at doses up to 1000mg/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 500mg/kg/day. This NOAEL is about 4 orders of magnitude above the expected exposure level arising from use of the spray; there are thus no concerns regarding developmental toxicity.

(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 some 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.

(vii) 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. However we recommend that monitoring of experience-in-use be continued.

COT statement 2004/06
November 2004

References

1. Clay P. Nonivamide (PAVA) In-vivo rat liver Unscheduled DNA synthesis assay. Central Toxicology Laboratory report CTL/SR1166, 13 June 2003.

2. PAVA (nonivamide); Local lymph node assay. Inveresk Report No 22133 (2003). Unpublished report. Commissioned by Sussex Police.

3. PAVA (nonivamide); Preliminary oral gavage pre-natal developmental toxicity study in the rat. SafePharm Laboratories Project No 1833/001 (2003). Unpublished report. Commissioned by Sussex Police.

4. PAVA (nonivamide); Oral gavage prenatal developmental toxicity study in the rat. SafePharm Laboratories Project No 1833/002 (2003). Unpublished report. Commissioned by Sussex Police.

5. Experience of use of PAVA incapacitant spray. Unpublished information; Sussex Police (2004).

6. Letter from Boehringer Ingelheim on human clinical experience of dermal preparations containing nonivamide (2004).

7. Letter from Beisdorf AG on human clinical experience of dermal preparations containing nonivamide (2004).

8. Letter from the Medicines and Healthcare Products Regulatory Agency Pharmacovigilance service on reported suspected adverse reactions associated with nonivamide and skin disorders. (2004).

9. Committee on Mutagenicity conclusions on mutagenicity data. February 2004. Available at http://www.advisorybodies.doh.gov.uk/com/.