The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CHLOROFORM

SUMMARY REPORT

1. No information about the use of chloroform in the target species, the routes of administration or the indications was provided.

2. Chloroform is a very volatile liquid which has been used as an inhalation anaesthetic, in topical analgesic preparations, as a therapeutic or non therapeutic ingredient in various oral medications and as an antitussive.

3. Chloroform depresses Central Nervous System function. It also has a direct depressant effect on the cardiac muscle.

4. Chloroform is used in human and veterinary medicine in a number of cough suppressant mixtures at a dose equivalent to 0.0042 ml/kg.

5. No information on other pharmacodynamic aspects of chloroform was available.

6. After oral administration of 100 mg/kg to rats and 150 mg/kg to mice of radio labelled chloroform a half-life of 0.8 and 2 hours was calculated for rats and mice respectively. No other information on distribution could be used, as the tissue concentrations were not quantified.

7. Pharmacokinetics of chloroform on the target species have not been investigated.

8. Oral LD_{50} values in the rat were in the range of 1000-1300 mg/kg.

9. Inhalation exposure of female mice and rats for 6 hours per day for 7 days to 0, 1, 3, 10, 30, 100 or 300 ppm of chloroform resulted in concentration-dependent lesions in nasal passages (increased epithelial mucosubstances).

10. The prolonged administration of chloroform in inhalation anaesthesia may be followed by fatty degeneration of the liver, heart and kidneys. Studies in mice administered by intraperitoneal or subcutaneous injections at doses of 50 to 1000 µl/kg indicated that nephrotoxicity could be detected as early as 2 hours after chloroform administration.

11. There are indications that chloroform may cause toxic effects in pregnancy and a higher frequency of chromosomal disturbances in occupationally exposed women and their children exposed *in utero*.

12. The use of chloroform as an anaesthetic in human medicine has been discontinued.

13. In animal studies chloroform causes embryolethality, foetotoxicity and malformations in doses lower than those causing maternal toxicity. Inhalation of 100 or 300 ppm of chloroform caused a higher incidence of foetal resorption and retardation of foetal development as well as low incidence of foetal anomalies.

14. Chloroform was not mutagenic in the Ames test, and in other *in vitro* assays. However, in a study of acute and subacute cytogenetic effects chloroform showed effects on rat bone marrow cells *in vivo* and it showed positive results in inducing chromosome aberration. An increased incidence of mouse sperm abnormalities with chloroform exposure has been reported and the

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above findings suggest that *in vivo* activation of chloroform may be necessary for mutagenic activity.

15. Studies conducted by the National Cancer Institute (USA) have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumours in male rat. Specific information of the dosages employed has not been provided.

16. No residue file has been provided.

Conclusions and recommendation

Having considered the :

- carcinogenic properties of choroform,
- equivocal data on mutagenicity,
- embryotoxicity and foetotoxicity,
- lack of information on pharmacokinetics and residue depletion,
- potential risk for the health of the consumer;

the Committee recommends the inclusion of chloroform in Annex IV of Council Regulation (EEC) No 2377/90.