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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CETRIMIDE

SUMMARY REPORT

1. Cetrimide (CAS 8044-71-1) is a quaternary ammonium antiseptic and surfactant. It consists mostly of trimethyltetradecylammonium bromide (CAS 1119-97-7; also known as tetradonium bromide) with smaller amounts of dodecyltrimethylammonium bromide (CAS 1119-94-4; also known as DTAB) and hexadecyltrimethylammonium bromide (CAS 57-09-0). The European Pharmacopoeia requires that cetrimide should contain at least 96% but no more than 101.0% alkyltrimethylammonium bromides.

2. Historically, the name cetrimide was used for a material consisting of predominantly hexadecyltrimethylammonium bromide, (CAS 57-09-0; also known as cetrimonium bromide, CTAB, and cetyltrimethylammonium bromide), together with smaller amounts of analogous alkyltrimethylammonium bromides. Some of the safety studies were carried out using this "cetrimide" rather than the cetrimide currently specified in the Europeam Pharmacopoeia.

3. In veterinary medicine, cetrimide is used as a topical antiseptic at concentrations of up to 2%. It is also used as an excipient in an injectable antibiotic formulation intended for use in cattle, sheep and pigs. When used as excipient, the concentration of cetrimide in the formulation is around 0.25 mg/ml, resulting in a dose of approximately 0.01 mg/kg bw of cetrimide in the target species.

4. In aqueous solution, cetrimide dissociates to a biologically-active cation and an inactive anion. Cetrimide is inactive towards bacterial spores, it is effective against some viruses and has variable anti-fungal activity. The cation is also responsible for the surfactant activity.

5. Cetrimide has a chemical structure similar to that of acetyl choline. It is a partial agonist and has depolarising muscle relaxant activities. At toxic dose levels, paralysis of the respiratory muscles leads to dyspnoea and cyanosis. Central nervous system depression may also occur.

6. Cetrimide has been shown to inhibit the intestinal absorption of substances such as D-glucose, methionine and sodium butyrate in several animal species. Interference with glucose absorption has also been reported in humans; the pharmacological mechanism is not known but is thought to involve action on receptor sites involved in the absorption process.

7. Cetrimide was poorly absorbed from the gastro-intestinal tract of rats. Female Sprague-Dawley rats were given a single oral dose of 0.8 mg/kg bw ^{14}C-cetrimide (predominantly hexadecytrimethylammonium bromide). Plasma concentrations peaked at around 5 µg/l, 4 hours after dosing and declined to around the limit of detection 48 hours after dosing. Residues in skeletal muscle plateaued at approximately 5 µg/kg over the period 8-72 hours after dosing before declining.

   Residues in liver and kidney peaked at around 125 and 50 µg/kg around 8 hours after dosing and fell to concentrations around the limit of detection 96 hours after dosing. 8 hours after dosing, 80% of the administered dose was recovered from the gastrointestinal tract; 87% of this being in the gastrointestinal tract contents. 2% of the administered dose was excreted in bile during the first 12 hours after dosing. After 3 days, 92% of the administered dose was excreted in the faeces and only 1% in the urine. Over 85% of the material in excreta was unmetabolised cetrimide.

8. Cetrimide binds strongly to collagen and keratin to form cetrimide : protein complexes. Consequently there is no significant absorption after dermal application of products containing low concentrations of cetrimide.

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9. As part of a teratology study, the amounts of ^{14}C-cetrimide were determined in maternal blood, liver, placentas, foetuses and foetal livers, 1, 8 and 24 hours after intraperitoneal administration to pregnant mice. 8 hours after treatment, 0,5% of the dose was present in the foetuses, 50% of this being in the liver, 3% of the administered dose was found in the placenta, 1 hour after administration. The concentration of radioactivity in the foetuses was <10% that found in the placenta indicating poor placental transfer.

10. Cetrimide was shown to be of moderate to high acute toxicity. The acute oral LD_{50} in the rat was 1000 mg/kg bw. The acute subcutaneous LD50 in the mouse was 75-80 mg/kg bw. The reported intraperitoneal LD_{50} values were inconsistent and ranged from 2-106 mg/kg bw in mice; the identity of the substance examined in these studies was not always clear.

11. Cetrimide was administered to groups of rats in the drinking water at dose levels of 0, 25 or 50 mg/kg bw per day for 21 days. There was a dose-related reduction in bodyweight gain and food consumption. No haematology, clinical chemistry or pathological examinations were carried out.

12. 2 repeated-dose toxicity studies were carried out in mice using oral administration. The "cetrimide" used in these studies consisted predominantly of hexadecyltrimethylammomium bromide. In one study, mice were given daily oral doses of 5 or 25 mg/kg bw "cetrimide" in aqueous solution, 6 days per week for 5 months. Bodyweights and haematology values were monitored twice a week. The bodyweight gain was reduced at both dose levels and erythrocyte counts were increased in the group receiving 25 mg/kg bw. There were no substance-related pathological findings. In another study, "cetrimide" as the stearate, rather than the bromide, was administered in the diet at doses of 0.025%, 0.05%, 0.1%, 0.2%, 0.4% or 0.5%. Substance-related deaths occurred at doses of 0.05% and above. There was a dose-related reduction in bodyweight gain at 0.1% and above. Cetrimide had an effect on the mucosal cells of the villi of the pyloric, duodenal and jejunal regions of the gastrointestinal tract. Haemorrhages in the gastrointestinal tract from the pyloric region of the stomach to the ileum were observed at 0.4% and 0.5%. Hypertrophy and hyperplasia of the duodenum and jejunum were observed at doses of 0.05% and above. No substance-related effects were observed in adult mice given the lowest dose level of 0.025% for 6 months (equivalent to approximately 35 mg/kg bw per day); however this dose resulted in significantly reduced bodyweight gain in immature mice. No results of haematology or clinical chemistry investigations in mice were reported in this study. The repeated-dose studies were inadequately carried out and reported and it was not possible to deduce a NOEL from these studies.

13. Cetrimide formulations were generally well-tolerated by the target species. However cetrimide was too toxic to fish to be of any value in the treatment of bacterial gill diseases.

14. Pregnant female NMRI mice were given a single intraperitoneal injection of 0, 10.5 or 35 mg/kg bw cetrimide (predominantly hexadecyltrimetylammonium bromide) on day 8, 10, 12 or 14 of gestation. There was no significant effect on maternal bodyweight gain. The numbers of dead foetuses were significantly increased in all groups given 35 mg/kg bw. There was a dose-related increase in the incidence of malformations, mostly cleft palate. The highest incidence of cleft palate occurred following administration on days 12 and 14 of gestation. Foetal bodyweights were also reduced following administration of the substance on days 12 and 14 of gestation. No NOEL was established in this study. No information was provided concerning possible reproductive effects after oral administration. The topical use of cetrimide in humans over many years has not been linked to any adverse reproductive effects. Products containing cetrimide are not contra-indicated in humans during pregnancy and lactation.

15. According to a brief published report, cetrimide was not mutagenic in an *in vitro* bacterial assay for gene mutation in *Salmonella tlyphimurium* TA 1535 and TA 1538. No carcinogenicity studies were carried out with cetrimide. Further data were not considered necessary due to the lack of mutagenic and carcinogenic potential of the quaternary ammonium compounds.

16. *In vitro* MIC values were determined for a range for bacteria including some species which may be found in the human gut flora. The MICs for *Pseudomonas* spp. were in the range 600-1250 µg/ml, for *Proteus* species : 250-500 µg/ml, and for *E. coli :* 50-150 µg/ml. Over 100 different hospital strains of each of these species were studied. The antimicrobial activity of cetrimide was significantly diminished by contact with biological materials such as protein and blood. Consequently any potential residues of cetrimide in foods of animal origin will not have any significant effect on the human gut flora.

17. Cetrimide has been used extensively in humans since 1942. Most formulations are intended for topical use, for cleansing skin, wounds and burns and for the treatment of nappy rash and acne. The aqueous solutions and creams which are used as a skin cleansers and antiseptics contain in the region of 0.1-1.0% cetrimide. Concentrations in the range 1-3% are used in shampoos to remove the scales of seborrhea. Cetrimide is also used as a preservative in eye drops and in disinfecting solutions for hard contact lenses. The topical preparations are associated with an extremely low incidence of adverse reactions; there have been occasional reports of skin irritation and some patients become hypersensitive after repeated application.

18. No residues depletion studies were carried out with cetrimide. Cetrimide is not absorbed after percutaneous administration and so the topical use of the substance should not result in significant residues in foods of animal origin. The use of cetrimide as an excipient in injectable formulations results in a dose of only 0.01 mg/kg bw in the target species. Taking into account the low toxicity of cetrimide and its poor absorption from the gastrointestinal tract, it may be concluded that the use of cetrimide in food producing species is unlikely to result in residues in food of animal origin at concentrations which are toxicologically relevant for the safety of consumers.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances into Annex II of Council Regulation (EEC) No 2377/90, and in particular that :

- cetrimide is poorly absorbed from the gastrointestinal tract and is quickly excreted;
- cetrimide is not significantly absorbed after percutaneous administration;
- topically-applied cetrimide has a long history of safe use in human medicine;
- the use of cetrimide in food producing species should not result in residues in food of animal origin at concentrations which are toxicologically relevant for the safety of consumers.

The Committee considers that there is no need to establish an MRL for cetrimide and recommends its inclusion into Annex II of Council Regulation (EEC) No 2377/90 for cetrimide in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Cetrimide	All food producing species	