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

EMEA/MRL/394/98-FINAL
April 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

AMMONIUM CHLORIDE

SUMMARY REPORT

1. Ammonium chloride (NH_4Cl, CAS no. 12125-02-9) is used in veterinary medicine, the major therapeutic use is as an urine acidifier in animals with urinary tract infection, for which purpose it is usually administered orally. It is also used as a systemic acidifier in animals with alkalosis; in emergencies it may be given intravenously as a 1 or 2% solution. It is used for prevention of urolithiasis in feeder steers at the recommended daily dose 200 mg/kg bw orally in the feed. In addition to its acidifying capacity ammonium chloride is employed as an expectorant, the recommended oral dosage for horses being 4 to 15 g/animal every 12 to 24 hours. The substance is a frequent ingredient of cough remedies intended for animals as well as humans. Ammonium chloride is used in some EU Member States incorporated in various forms of sweets. Some ammonium salts, notably the acetate, the carbonate and the bicarbonate, are used to adjust or buffer the pH of foods. Ammonium chloride is also authorised as a feed additive.

2. The ammonium ion (NH_4^+) is converted to urea in the liver, the liberated proton accounting for the systemic acidifying effect of the substance. In the kidney of healthy animals ammonia (NH_3) is formed *de novo* by deamination of glutamine and other amino acids and excreted as NH_4^+ with the ultrafiltrate. Due to its rather poor diffusion potential a major part of ammonium stays in the urine thereby decreasing the pH.

   Ammonium chloride and several other ammonium salts are classified as expectorants. They are assumed to increase airway mucous secretion by a reflex action from the ventricle. However, their value as expectorants seems questionable.

3. Ammonium chloride is absorbed from the gastrointestinal tract, especially from the colon where the pH shifts the balance between NH_3 and NH_4^+ in favour of NH_3. Systemically absorbed ammonia is converted to urea, the major part of which is excreted via the kidney, but approximately 20% (in humans) defuse into the gut and pass on to the colon where it is broken down by microbial action to ammonia which is subsequently reabsorbed. In the kidney of healthy animals NH_3 is formed *de novo* by deamination of glutamine and other amino acids as part of the acid-base regulatory mechanism, at normal pH NH_4^+ predominates. In adult humans the estimated daily urinary excretion of NH_4^+ salts is equivalent to approximately 1200 mg ammonium.

4. Ammonium chloride in toxic doses will produce an syndrome clinically characterised by dyspnea, muscle fasciculation, convulsions and terminating in acute pulmonary oedema. In farm animals doses of 300 to 500 mg/kg bw orally will usually cause clinical signs of toxicosis. In most species the minimal lethal dose is 500 to 1500 mg/kg bw; horses seem to be somewhat less susceptible (minimal lethal dose 4000 mg/kg bw). The toxic effects observed are assumed mainly to be caused by NH_3 directly.

5. No data have been presented concerning the toxic effects following repeated exposure.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

6. No data concerning reproductive effects have been provided.

7. No data concerning the mutagenic and carcinogenic potential of the substance have been provided.

8. NH_3 and NH_4^+ are normal by-products of the microbiological breakdown of proteins and urea in the gastrointestinal tract and the catabolism of amino acids in the liver. Smaller amounts result from breakdown of amino acids in peripheral tissues. Endogenous and systemically absorbed NH_3 is converted to urea in the liver, the majority of which is quickly eliminated via the kidney. It therefore appears unlikely that concentrations of NH_3 and NH_4^+ achievable in edible tissues following recommended therapeutic or prophylactic use of ammonium chloride will pose any risk to the health of the consumer. In addition, ammonium chloride is used as a urinary acidifier in humans, the recommended oral dosage being 1 to 2 g/person every 4 to 6 hours.

9. At its 26th meeting the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered it unnecessary to establish ADIs for ammonium acetate, ammonium carbonate and ammonium bicarbonate, as the estimated total daily intake of each in food did not represent a hazard to consumer health.

Conclusions and recommendation

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

- the concentrations of NH_3 and NH_4^+ likely to occur in edible tissues of food producing animals following recommended therapeutic or prophylactic use of ammonium chloride will pose no significant risk to the health of the consumer,
- the treated animals are unlikely to be sent for slaughter during or immediately after treatment;

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

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