Summary Report, by Commitee For Veterinary Medicinal Products Humic Acids and Their Sodium Salts

Summary:
1. Humic acids are a class of compounds resulting from decomposition of organic matter, particularly plants, and are natural components of drinking water, soil and lignite. They are three dimensional macrocolloidal molecules with a polyaromatic center containing iso- and heterocyclic structures and peripheral side-chains. The humic acids under consideration are extracted from lignite (brown coal) and have an average moleculer mass of 20000 to 150000. They include humocarb with a humic acid content of 55?10%, concentrated humic acid and a humic acid-iron (II)-carboxymethylcellulose-complex.

Humic acids are used in horses, ruminants, swine and poultry at a oral doses level of 500 to 2000 mg/kg bw for the treatment of diarrhoea, dyspepsia and acute intoxications. They exert an protective action on the mucosa of the intestine and have antiphylogistic, adsorbtive, antitoxic and antimicrobial properties. They are not used in humans.

2.The intramusculer injection of the humic acid sodium salt (1 mg/kg bw) to rabbits and had no effects on haematological parameters and the glucose concentration in blood, but affected the albumine/globuline ratio in plasma (marked increase of the gammaglobuline fraction).

3.The absorbtion of humic acids from the intestine after oral administration is very low. The rate of absorbtion in the isolated gastrointestinal tract of the rat ranged from less than 0.05 to 0.07 %.

4.Humic acids are of low toxicity after oral administration. The LD50 in rats is greater than 11500 mg/kg bw. However they are toxic after parenteral administration in mice and 163.5 to 205.8 mg/kg bw after intraperitoneal administration in rats.

5.In a 30-day toxicity study in rats oral dose levels of 100 mg/kg bw/day of concentrated humic acid or of its sodium salt had no effects on the behaviour and induced no clinical disturbances. The same results were obtained in dogs which received daily doses of 300 mg/kg bw for 90 days. Humocarb or concentrated humic acid administrated with feed for 90 days at the dose of 1000 mg/kg bw/day had no effects on the pH in the gastrointestinal tract of rats and rabbits.

6.Groups of 10 pregnant rats were treated orally with 5000 sodium humate/kg bw/day on days 5 to 17 of pregnancy or with 1000 mg/kg bw/day on days 5 to 9 or on days 11 to 15 of pregnancy . No teratogenic effects were seen.. After intraperitoneal administration of 50 mg/kg bw/day on days 5 to 9, days 11 to 15 or days 5 to 17 of pregnancy the resorption rate was higher (13.2 to 13.6 %) than in negative controls (3.2 %). No teratogenic effects were noted.

7.The concentrated humic acid (50 to 150 mg/ml) and the sodium salt (500 to 15000 mg/ml) did not induce an increase of spontaneous aberrations in kidney cells of rabbits and baby hamsters or in diploid human fibroblasts. Both formulations had no mutagenic acitivity in Salmonella typhimurium TA98 and TA100 in concentrations between 0.1 and 0.5 % with and without metabolic activation. It can be concluded that humic acids are not mutagenic.

8.No carcinogenicty studies were provided. Considering the structure of the substance, the fact that long-term administration gave no indications for a carcinogenic potential of the

compounds and that they are devoid of mutagenic activity in the test systems used, such data are not required.

9.In residues studies swine orally received a mixture of humocarb and concentrated humic acid (ratio 16:1) at a dose level of 500 (n=2) and 2000 mg/kg bw/day (n=3) for 30 days and sheep (n=3) orally received 1000 to 2000 mg/kg bw/day. At the end of the treatment periods no humic acid could be detected by a photometric method (liimit of detection : 10 to 50 mg/ml) in blood plasma and muscle, liver and kidney. However, due to the inadequcies of the analytical method the results are of limit relevance.

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 in particular that:

- humic acids are part of the human diet as they are contained in drinking water
- humic acids have low oral toxicity
- humic acids are poorly absorbed after oral administration
- humic acids are used for infrequent and non-regular treatments;

The Committee concludes that there no need to establish an MRL for humic acids and their sodium salts and recommends their 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
Humic acids and their sodium salts	All food producing species	For oral use only

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Establishment of Maximum Residue Limits for Old Substances in Veterinary Medicines Marketed in the European Union prior to 1 January 1992:
Workplan of CVMP Safety of Residues Working Party

The EMEA in consultation with the CVMP and its Safety of Residues Working Party, has for sometime now been adhering to a detailed workplan in order to ensure a timely and structured approach to completing the assessments of old substances to establish Maximum Residue Limits (MRLs), by the new deadline of 1 January 2000 set out in Council Regulation (EEC) 434/97. The success of completing such a workplan is contingent on provision of satisfactory responses by the applicant to requests of additional information set out in the CVMP list of questions. In addition, the Agency is cognisant of the important issues relating to the Availability of Veterinary Medicines in the European Union, and the potential for the loss of some medicinal products because MRLs for certain substances used in such medicines may not be established before the deadline of 1 January 2000.

As a consequence the Agency has recently been in consultation with industry through its European association, FEDESA, as to how increased awareness can be achieved as to the progress being made in setting MRLs for the remaining old substances according to the

workplan. With the full agreement of FEDESA this workplan of the Safety of Residues Working Party is now being published so that applicants and all interested parties can become fully aware of the likely timetable for completion of the assessments. The workplan itself is attached and lists the status of those substances currently in the assessment process in the Safety of Residue Working Party (Annex I).

In addition information is being provided on those substances whose assessment by the working party has been completed, and proposal sent to the CVMP for consideration (Annex II). However, it should be noted that the CVMP may conclude that for certain substances in this list an MRL can not be established because of the inadequacy of the data provided by the applicant A list of substances for which the CVMP has completed its assessment is also being provided (Annex III). This list includes those substances which have been considered by the CVMP and whose recommendations have now been sent to the Commission. It should be noted that following the consultation process undertaken by the Commission, recommendation by the CVMP may still not be endorsed for certain substances. The list also includes some substances for which the CVMP was unable to establish an MRL because of the inadequacy of the data supplied by the applicant.

Notice is also drawn to the fact that during the process of evaluating applications to set MRLs for the old substances some companies have elected not to continue to defend their substances. Such applications have either been withdrawn or are no longer supported. These substances do not appear on any of the annexes to this bulletin.

Attention is drawn to the fact that the defended substances of vegetable origin and homeopathic substances still under consideration are not included in this workplan.

Any enquiries regarding this connection maybe directed to the attention of Dr. Kornelia Grain, Head of MRL Sector at the EMEA, 7 Westferry Circus, Canary Wharf, London E14 4HB, telephone + 4 171 418 84 32

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