TEBUFENOZIDE (addendum)

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Explanation

Tebufenozide was first evaluated by the 1996 JMPR, which established an acceptable daily intake (ADI) of 0–0.02 mg/kg of feed on the basis of a no-observed-adverse-effect level (NOAEL) for haematotoxicity of 50 mg/kg, (equal to 1.8 mg/kg bw per day) in a 1-year study in dogs, and of 25 mg/kg (equal to 1.6 mg/kg bw per day) in a two-generation study of reproductive toxicity in rats. At the 1999 JMPR, it was recommended that the acute toxicity of tebufenozide be evaluated as soon as possible. The 2001 JMPR evaluated the acute toxicity of tebufenozide on the basis of the available data. The Meeting established an acute reference dose (RfD) of 0.05 mg/kg bw on the basis of a NOAEL of 5 mg/kg bw per day for haematotoxicity in a 2-week study in dogs. The Meeting noted that it might be possible to refine this estimate using the results of a study designed specifically for this purpose. After data from such a study was submitted, the present Meeting reconsidered the acute RfD for tebufenozide.

Evaluation for acute reference dose

The JMPR in 1996 noted that the LD_{50} of tebufenozide was >5000 mg/kg bw in mice and rats treated orally, and that toxicity after dermal application in mice and rats or inhalation in mice was also low (dermal LD_{50}, >5000 mg/kg bw; inhalation LC_{50}, >4.3 mg/l of air)

In short-term studies of toxicity, the main effect in mice, rats, and dogs given diets containing tebufenozide was haemotoxicity, with signs of regenerative haemolytic anaemia and compensatory responses in haematopoietic tissues. Dogs were the most sensitive species, with effects being seen after 2 weeks, the shortest interval investigated. In rabbits treated by gavage on days 7–19 of gestation, no signs of maternal toxicity, embryo- or fetotoxicity or teratogenicity were observed at a dose of up to 1000 mg/kg bw per day, the highest dose tested. Similar findings were made in studies of developmental toxicity in rats, in which the NOAEL was also 1000 mg/kg bw per day, the highest dose tested. The 1996 JMPR concluded that tebufenozide and its metabolites are not genotoxic.

Acute haemotoxicity in dogs

A study of acute haemotoxicity in dogs was performed in compliance with good laboratory practice (GLP), with the exception that the test diet was not analysed for confirmation of dose or for homogeneity. There are no applicable guidelines for the design of such a study. Groups of four male beagle dogs were given diets containing technical-grade tebufenozide (purity, 99.0%) at a concentration of 1.08 or 4.30 g/kg (1080 or 4300 mg/kg) for 9 h. These concentrations correspond to mean achieved intakes of 21.9 and 89.4 mg/kg bw. Control animals received normal diet. The homogeneity, stability and concentration of the test material were not investigated in this study. All animals were observed twice per day, and body weight was recorded 2 days before the start of the study and on days 8 and 15. Food consumption was recorded on the first day of the study in the two treated groups only. Five days before treatment and on day 1 (before dosing), day 2 (24 h after exposure), day 8 and day 15, blood samples from the jugular vein of fasted animals were taken for haematology and limited blood chemistry (erythrocyte volume fraction, haemoglobin concentration, erythrocyte count, methaemoglobin, Heinz bodies, reticulocytes, platelet count, erythrocyte morphology, erythrocyte indices (mean corpuscular haemoglobin; mean corpuscular volume; mean corpuscular haemoglobin concentration; and total bilirubin). No ophthalmological examinations, necropsy or histopathology were undertaken in this study (for humane reasons; the animals were reassigned after this study).

All the animals survived until the end of the observation period. There were no treatment-related observations during the study. The sporadic occurrence of soft faeces observed in one animal at the highest dose was not considered to be treatment-related, as it had also occurred in this animal before treatment. There was no effect of treatment on body weight; animals in all three groups (except two of the dogs at the highest dose) exhibited minor weight loss over the duration of the study. There were no obvious or statistically significant treatment-related changes in any of the haematological parameters, methaemoglobin formation or serum concentrations of total bilirubin.

The NOAEL was 89.4 mg/kg bw, the highest dose tested, on the basis of clinical observations, haematology, methaemoglobin formation and serum concentration of total bilirubin (Stebbins et al., 2002).

Comments

Tebufenozide has low acute toxicity in rats and mice after oral (LD_{50} > 5000 mg/kg bw) or dermal (LD_{50} > 5000 mg/kg bw) exposure, and in rats after exposure by inhalation (LC_{50} > 4.3 mg/l of air). In short-term studies of toxicity in mice, rats and dogs, the main effect was haematotoxicity, with signs of regenerative haemolytic anaemia and compensatory responses in haematopoietic tissues, accompanied by the formation of methaemoglobin. The dog was the most sensitive species, males showing slightly greater changes in several parameters than females (methaemoglobin, reticulocytes and Heinz bodies).

In the study evaluated by the present Meeting, male beagle dogs received tebufenozide in the diet such that intakes of 21.9 and 89 mg/kg bw were achieved. Animals were permitted 9 h to consume the test meal. The diet was not tested for homogeneity, stability or concentration of the test substance but, given the duration of the treatment period, this was not considered to be a serious limitation of the study. No necropsy or histopathology was undertaken, but the study design was adequate for the evaluation of the acute haematotoxicity of

tebufenozide. Blood samples were taken before, and 2, 8 and 15 days after exposure to tebufenozide. Treatment with tebufenozide had no significant effect on clinical signs or haematological parameters, including reticulocyte numbers or concentrations of serum total bilirubin. The NOAEL was 89.4 mg/kg bw, the highest dose tested.

On the basis of studies evaluated previously by the Meeting, it was concluded that tebufenozide and its metabolites are not genotoxic. It was also concluded that tebufenozide is not embryo- or fetotoxic, or teratogenic in rats or rabbits at a dose of up to 1000 mg/kg bw per day.

Toxicological evaluation

The Meeting considered that the study in dogs was adequate for the establishment of an acute RfD for tebufenozide. Accordingly, an acute RfD of 0.9 mg/kg bw was established, based on a NOAEL of 89.4 mg/kg bw (the highest dose tested) and a safety factor of 100.

Reference

Stebbins, K.E., Radtke, B.J. & Baker, P.C. (2002) Tebufenozide: Acute red blood cell evaluation in beagle dogs. Unpublished report of study ID 021104 from Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, USA. Submitted to WHO by Dow AgroScience LLC, Indianapolis, IN, USA.