COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

AMITRAZ

SUMMARY REPORT (2)

1. Amitraz had been previously assessed according to the requirements of Council Regulation (EEC) N° 2377/90. The measures taken according to this assessment had been published in Commission Regulation (EEC) N° 3093/92.

2. A provisional ADI of 0 - 0.003 mg/kg bw and provisional MRLs for porcine muscle of 0.05 mg/kg and for liver and kidney of 0.2 mg/kg based on the sum of amitraz and metabolites containing the 2,4-dimethylaniline moiety, were established. A time period terminating on 1 July 1994 was applied to the provisional MRLs.

3. Information to complete the toxicological evaluation and residue depletion data, including validated analytical methods, was required.

4. Dossiers addressing the questions raised in the previous evaluation of amitraz by the CVMP were received from industry and evaluated in relation to the expiry of the provisional MRLs for porcine tissues.

5. Amitraz is a formamidine acaricide and insecticide used on top fruit, cotton and hops and as veterinary medicine for the treatment of ectoparasites in a number of food producing animals.

6. Amitraz interacts with octopamine receptors in the central nervous system of ectoparasites, inducing increased neuronal activity, abnormal behaviour, detachment and death. It also possesses -2-adrenoreceptor agonist activity.

7. Amitraz is rapidly and well absorbed after oral administration and eliminated from most tissues within a few days. Amitraz is rapidly metabolized and excreted, mainly in the urine. The metabolism of amitraz is qualitatively similar in the rat, mouse, cat, dog, baboon, cow and human, proceeding via hydrolysis to N-(2,4-dimethylphenyl)-N'-methyl formamidine (BTS 27271) and 2,4-dimethyl formanilide (BTS 27919). These metabolites still contain the 2,4-dimethylaniline (2,4-DMA) moiety. The end product is 4-amino-3-methylbenzoic acid (BTS 28369) which is rapidly conjugated and excreted. Amitraz is poorly absorbed by the dermal route.

8. Administered orally, amitraz is of moderate to low toxicity in acute toxicity tests with rats and mice. The LD50-values in rats and mice are respectively 400-938 and >1600 mg/kb bw. Amitraz is of low toxicity after inhalation in rats (LC50 is 65 mg/l). Acute toxicity effects from amitraz treatment include lethargy, hyperexitability, CNS depression, and hypothermia.

9. In a number of subchronic oral toxicity studies with amitraz in mice, rats and dogs, dogs appeared to be the most sensitive species with CNS depression as the most predominant effect (NOEL 0.25 mg/kg bw/day). Subchronic toxicity studies with metabolites of amitraz showed that BTS 25369 is far less toxic, while the toxicity of BTS 27271 on a molar base is comparable to that of the parent compound.

10. From reproduction toxicity studies with rats (1- and 3-generation) and teratogenicity studies with rats and rabbits it was shown that amitraz influences mean litter size and viability of the young in doses that were toxic to the dams. Amitraz showed no teratogenic potential. The overall NOEL for developmental toxicity was 1.5 mg/kg bw/day.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

11. In an adequate set of in vitro and in vivo mutagenicity tests, covering different genotoxic endpoints, amitraz and metabolites were regarded as non-genotoxic. In carcinogenicity studies with mice and rats amitraz was regarded as non-carcinogenic (the increased incidence of hepatocellular tumours in female mice was not considered to be of relevance to human health).

12. From a double blind randomized cross-over study with male volunteers receiving single doses of 0.0625 or 0.125 mg amitraz/kg bw, a NOEL of 0.125 mg/kg bw could be established.

    Based on the NOEL of 0.25 mg/kg bw/day from the 2-year dog study, and using a safety factor of 100, an ADI of 0.003 mg/kg bw can be established. This ADI is in accordance with the ADI established by the JMPR (1984, 1990) based on the same toxicity data.

13. Part of the ADI for amitraz (about 70%) is already occupied for consumption of food commodities of plant origin since amitraz is also used for plant protection purposes. This leaves 30% of the ADI, 54 µg/day for a 60 kg person, for products of animal origin.

14. In pigs, residues can be found in all tissues after topical administration (spray or pour-on) of amitraz. After repeated spraying over the entire body surface, the highest residue concentrations were found in skin + subcutaneous fat (declining from 1.6 ppm amitraz equivalents after a withdrawal time of 1 day, to 0.013 ppm at day 21). Lower levels were found in liver, kidney, muscle and renal fat (0.012 - 0.03 ppm at day 1). Also repeated pour-on administration on the dorsal mid-line of the animals revealed the highest residue concentrations in processed skin (declining from 1 ppm amitraz equivalents after a withdrawal time of 1 day, to 0.08 ppm at day 14 and 21). Lower levels were found in liver (0.3 ppm at day 1, 0.22 ppm at day 3 and < 0.1 ppm thereafter), kidney (0.24 ppm at day 1 and < 0.08 ppm thereafter), muscle and fat (<0.1 ppm at all time points).

15. The routine analytical method for the determination of residues of amitraz in porcine tissues (total 2,4 dimethylaniline procedure) is well described, experimental data about the sensitivity, specificity, repeatability and reproducibility are still lacking. Also a confirmative method has not been provided so far.

16. According to article 4 of Council Regulation (EEC) N° 2377/90, in order to allow for the completion of these studies in progress addressing the outstanding questions, the time period applying for the provisional MRLs for porcine tissues is extended until 1 July 1996. The submission of the further information is required before 1 July 1995.