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Toxicological evaluation of certain veterinary drug residues in food

Prepared by the
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On the basis of the results of studies of genotoxicity, ractopamine was considered to be a weak mutagen and clastogen in human lymphocytes and mouse lymphoma cells in vitro, while assays for chromosomal aberration in bone-marrow cells and for micronucleus formation in mice and rats indicated a lack of genotoxic effects in vivo. This conclusion is supported by the lack of genotoxically-induced tumours in studies of oncogenicity in rodents (Williams, 1998a, 1998b).

The Committee therefore considered that ractopamine is not genotoxic.

2.2.4 *Reproductive toxicity*

At its fortieth meeting, the Committee considered a two-generation study of reproductive and developmental performance in Sprague-Dawley rats treated with ractopamine. Significant embryotoxic effects and a minor teratogenic response were observed only at the highest dose of 150 mg/kg bw per day, at which maternal toxicity was also noted. The NOEL was 15 mg/kg bw per day (Williams & Hoyt, 1987; Annex 1, reference *105*).

A single-generation study of reproductive toxicity in crossbred swine was conducted to identify the adverse effects of feeding gilts with diets containing ractopamine during the finishing period. After withdrawal of ractopamine from the diet, the gilts were bred and allowed to farrow, and to nurse their litters. It was concluded that with ractopamine at the tested dietary concentrations of 20 and 60 mg/kg of feed, the reproductive performance of gilts would not be adversely affected after the drug was withdrawn (Williams, 1989). The study did not comply with appropriate standards for protocol and and was therefore not considered to be suitable for the assessment of the safety of residues of ractopamine.

2.2.5 *Special studies*

(a) Pharmacodynamic effects: β-adrenergic receptor selectivity for stereoisomers of ractopamine

Ractopamine is reported to be active at both β_1- and β_2-adrenoceptors. Results of previous studies suggest that racemic ractopamine is about 20 times more selective for β_1- versus β_2-adrenoceptors, as shown by values for binding affinity in rat glioma cells. This selectivity contrasts with the selectivity for β_2-adrenoceptors reported for other β-agonists that are effective in growth modification in rodents, such as clenbuterol or salbutamol. Furthermore, racemic ractopamine was shown to be almost equally effective with respect to the effective dose (ED_{50}) values reported for β_1-adrenergic cardiac effects and β_2-adrenergic bronchodilation and relaxation of costo-uterine muscle in vitro. The effects were submaximal in heart preparations and maximal in tracheal and costo-uterine muscle preparations when compared with the effects of isoproterenol (Williams et al., 1989; Anderson et al., 1993). Results from recently published studies indicate that the biologically most active RR isomer (butopamine) of ractopamine binds non-selectively to cloned porcine β_1- and β_2-adrenoceptors expressed in Chinese hamster ovary cells, but that adenylyl cyclase activation is more efficacious through the β_2-adrenoceptor. Among the ractopamine stereoisomers, butopamine has the