European Food Safety Authority

The EFSA Journal (2009) 1041, 1-52

SCIENTIFIC OPINION

Safety evaluation of ractopamine[1]

Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed

(Question No EFSA-Q-2008-433)

Adopted on 2 April 2009

PANEL MEMBERS*

Georges Bories, Paul Brantom, Joaquim Brufau de Barberà, Andrew Chesson, Pier Sandro Cocconcelli, Bogdan Debski, Noël Dierick, Jürgen Gropp, Ingrid Halle, Christer Hogstrand, Joop de Knecht, Lubomir Leng, Anne-Katrine Lundebye Haldorsen, Sven Lindgren, Alberto Mantovani, Miklós Mézes, Carlo Nebbia, Walter Rambeck, Guido Rychen, Atte von Wright and Pieter Wester

SUMMARY

Ractopamine hydrochloride is pharmacologically classified as a phenethanolamine β-adrenoceptor agonist. The use of the substance as a feed additive is authorised in different countries (USA, Canada, Japan and Mexico) for growth promotion of fattening pigs and cattle. Ractopamine has not been assessed in the EU so far.

Following a request from the European Commission, the European Food Safety Authority (EFSA) was asked to provide an opinion on the JECFA evaluation for ractopamine hydrochloride, having consulted and closely co-operated with other organisations such as EMEA and the Community Reference Laboratory responsible for β-agonists (BVL in Berlin).

The metabolic fate of ractopamine hydrochloride is similar in the target species (pig and cattle), laboratory animals and humans.

The FEEDAP Panel concluded from an acute study in dogs that tachycardia and peripheral vasodilatation observed are in line with the expected pharmacological action. From another acute study in dogs, with limited statistical power, a pharmacological NOAEL of 2 μg kg^{-1} bw could be derived.

Comparing dog and monkey data it appeared that the dog could be considered as more sensitive to ractopamine (β-adrenergic substances). However, the FEEDAP Panel considered that there was not enough data to support this conclusion.

NOAEL's derived from pharmacological repeated dose studies should not be regarded as a meaningful basis for an ADI because of the observed down regulation of lung β-adrenergic

[1] For citation purposes: Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) on a request from the European Commission on the safety evaluation of ractopamine. *The EFSA Journal* (2009) 1041, 1-52

* One member of the Panel did not participate in the discussion on the subject referred to above.

The FEEDAP Panel concludes that all treatment-related effects observed in the long-term studies in mice and rats were attributable to the β-adrenergic activity of ractopamine. It shares the JECFA and FDA opinion, that the induction of leiomyomas is a non-genotoxic event with a threshold and ractopamine is not a direct carcinogen. Considering all studies, the FEEDAP Panel concludes that ractopamine is not mutagenic and is unlikely to present a carcinogenic risk to consumers.

Since data in laboratory animals gave a wide range of NOAELs, the available human data was considered pivotal by JECFA as it is by the FEEDAP Panel when assessing consumer safety.

On the basis of mean values from the study with six healthy volunteers the JECFA established an ADI for ractopamine of 0–1 μg kg^{-1} bw per day based on the NOEL of 67 μg kg^{-1} bw and the application of a safety factor of 50, rounded to one significant figure.

The human study was originally designed as a preliminary (open label) study intended to establish dose-effect responses to enable suitable doses to be selected for a larger (double-blinded) study. It was not intended to define a no-effect level. The use of the data obtained for this purpose inevitably exposes experimental weaknesses and uncertainties and limits the conclusiveness of the study. The absence of a double-blinded study design to avoid placebo effects would introduce bias.

Significant subpopulations which may be at higher risk for adverse events after ß-adrenergic stimulation require particular consideration when estimating the safety factor. The FEEDAP Panel concludes that the safety factor applied by JECFA to derive the ADI from the NOEL does not sufficiently take into account population subsets at higher risk.

Each evaluation of the human study based on a group mean value is handicapped by the poor statistical power. The FEEDAP Panel notes that an evaluation should be based on the individual response (pharmacodynamic effects). This has been done for the lowest administered dose (5 mg per subject). The FEEDAP Panel concludes that the 5 mg dose cannot be definitely considered a no-effect dose, although within this descriptive evaluation random effects cannot be clearly distinguished from systematic effects.

The FEEDAP Panel also examined the alternative of considering the 5 mg dose as a LOEL and, because data for doses between 5 and 0 mg are not available, to apply the benchmark procedure for determining a NOEL. The benchmark procedure did not allow establishing a NOEL (to exclude a 10 % change in the electromechanical systole (QS2), a 20 % change in heart rate and a 40 % change in cardiac output, the lower confidence limit of the benchmark dose would be 0 mg).

The FEEDAP Panel notes that if an ADI would be derived from a pharmacological study, a NOEL must be taken to consider not only clinically relevant ('adverse') effects in the consumer but also subjective discomfort even when occurring only for a short time.

Furthermore, the FEEDAP Panel is of the opinion that the uncertainties concerning the figure of a NOEL should not be balanced by a (higher) safety factor. All the uncertainties taken together would reach a dimension in which more or less arbitrary estimations prevail.

The FEEDAP Panel finally concludes that the human study cannot be taken as a basis to derive an ADI, as proposed by JECFA, and consequently no proposal for MRLs can be made.

The CVMP fully supported the conclusions of the FEEDAP Panel with regard to the safety evaluation of ractopamine.

The FEEDAP Panel proposes to use the sum of free ractopamine and ractopamine glucuronoconjugates (sensitive analytical methods available, NRCP of the EU), which is supported by CVMP, instead of free ractopamine as the marker substance.