

Notes on the claims of “unanswered safety questions” concerning ractopamine

1. Ractopamine has been evaluated three times by the Joint Expert Committee on Food Additives (JECFA), which is the independent body that Codex relies on for scientific advice:

- The 62nd JECFA (2004) established an Acceptable Daily Intake (ADI) for ractopamine and recommended Maximum Residue Limits (MRLs) in muscle, liver, kidney, and fat tissues in pigs and cattle.
- The 66th JECFA (2006) reevaluated the residue data and confirmed the previously recommended MRLs.
- In 2010, JECFA reviewed Chinese data on lung tissue, and concluded that the MRLs recommended for the other four tissues did not need to be revised.

2. Integrity of JECFA procedures

- Much of the JECFA evaluation of ractopamine was conducted under the principles and procedures outlined in the 1987 Environmental Health Criteria (EHC) 70. The current procedures for risk assessment used by JECFA are found in EHC 240, *Principles and Methods for the Risk Assessment of Chemicals in Food*, a joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization.
- The JECFA evaluation of ractopamine was in complete accord with the principles and procedures set out by EHC 70 and EHC 240. An objection to the JECFA ractopamine evaluation is equivalent to objecting to the entire foundation by which both JECFA and the Joint Meeting on Pesticide Residues (JMPR) conduct their evaluations, and essentially challenges the established MRLs for hundreds of food additives, contaminants, pesticides, and veterinary drugs.
- The JECFA approach to the evaluation of ractopamine was also entirely consistent with the approach for the evaluation of the safety of residues of veterinary drugs used in food producing animals developed by the VICH, which is a program of the EU, United States, and Japan, to harmonize technical requirements for approving veterinary drugs by regulatory authorities.

3. Concerning the independence of JECFA

- JECFA is organized by and operates under the FAO and WHO. Unlike Codex Committee participants, who represent their governments, JECFA participants do not represent governments or regions. JECFA participants are selected solely for their scientific expertise and experience. They must have an extensive publication record and experience in providing scientific advice, and they must declare any conflict of interest that would impair their impartiality.
- A JECFA committee typically consists of about 30 experts, assuring ample scrutiny of the recommendations before they are issued. Each Committee includes experts from several regions of the world. The qualifications required of JECFA experts are posted on the FAO and WHO JECFA web sites. These include technical expertise as well as lack of conflict of interest.

- Each JECFA Committee is convened separately. Thus, when there are re-evaluations of a drug—as was the case with ractopamine—the Committee is re-configured with new experts included.

4. Concerning the EFSA review

- In 2009, the European Commission asked its European Food Safety Authority (EFSA) to “establish if there were any scientific grounds for concern, in particular any information that would call into question the scientific grounds for the JECFA evaluation and/or the safety of food and food products from animals treated with ractopamine.”
- EFSA did not conduct a risk assessment and did not provide new scientific data, but rather reviewed the JECFA assessment based on the published report.
- EFSA criticized the JECFA process contending that the human study (1) “cannot be taken as a basis to derive an ADI” and was (2) “handicapped by the low statistical power.” Further, EFSA suggested that (3) a lower ADI could be derived from a study on dogs, and (4) the safety factor applied by JECFA was inadequate.

5. Concerning the Human Health Effects

- The studies considered by JECFA include a human study, supported by many other studies, and JECFA selected the human study for determining the NOEL and calculating an ADI. Ractopamine has been in use for over 12 years, and hundreds of millions of persons have routinely eaten meat from animals that were administered the drug. There is no credible indication of any human health effects in this population as a result of the labeled use of the drug.

6. Concerning the lower ADI that would result from the dog study

- Typically, the most sensitive species is used for the establishment of an ADI, unless there is data indicating that another species is more relevant to human exposure. In this case, both the human study and the primate study were more relevant to human exposure than the dog study, which even EFSA noted was not representative of the human response.
- JECFA believes that the human study is most appropriate for establishing the ADI, and the ractopamine study clearly showed that the dog study would not be appropriate. A lower No Observable Effect Level (NOEL) or Lowest Observed Effect Level (LOEL) could be set based on the dog study, but the human study clearly showed that the primate is a better animal model than the dog for the human response to ractopamine hydrochloride because, as JECFA noted, the metabolism of ractopamine in dogs was very different than in humans.
- The EFSA review largely ignored¹ the in-vitro studies and the studies in animals, including primates, which were considered in the JECFA evaluation. Much of the safety information for

¹ This study is noted in the EFSA report, but EFSA draws the unusual conclusion that a short acute study is more relevant. The EFSA focus on acute study effects is not inappropriate given the acute impact of beta-adrenergic drugs, including ractopamine, on cardiopulmonary endpoints.

addressing long-term exposure resides in the animal data. Furthermore, both chronic and acute effects are important considerations for evaluating ractopamine. The chronic primate study is also adequate for setting an ADI; there are cardiovascular measurements very early in exposure to the drug, as well as the long term effects. If used, the same ADI would result (when rounded to one significant figure as is Codex practice).

- According to the WHO JECFA Secretariat, JECFA, when evaluating compounds, generally applies an overall weight-of-evidence approach and reaches its conclusions considering all relevant studies. In the case of ractopamine, the ADI was established based on a human study, as the most relevant study for human health risk assessment. However, the most relevant animal studies (in Rhesus monkeys) were also considered and these supported this ADI.²

7. Concerning the statistical power issue

- Both the EHC 240 and the JECFA procedures note that a human study to be sufficient should have a minimum of five human participants. The study used in the ractopamine evaluation included six persons.

8. Concerning the safety factor and sensitive populations

- JECFA applied a safety factor of 50 to the NOEL (no observed effect level) to establish the ADI for ractopamine. It was lowered by a factor of 10 to account for possible differences between the sensitivity of experimental animals and humans. Another 5-fold factor was used to account for limitations in the study and for sensitive populations. This is a very conservative approach.

9. EFSA Agreement with JECFA: non-carcinogenic

- The EFSA evaluation agreed with JECFA on an important point: *“Considering all studies, the [EFSA] FEEDAP Panel concluded that ractopamine is not mutagenic and is not likely to present a carcinogenic risk to consumers.”*

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² Paragraph 18 from the Report of the 18th meeting of CCRVDF