CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 4.8 **CRD02**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION

Forty-fifth Session

FAO Headquarters, Rome, Italy

21-25 November and 12-13 December 2022

Responses of the FAO/WHO JECFA Secretariat to the issues that arose during the informal consultations on Zilpaterol by the Chair and Vice-Chairs of the CAC

The 44th Session of the Codex Alimentarius Commission (CAC44) tasked the Chairperson and Vice-Chairpersons of CAC (CVCs) "to undertake informal consultations with all relevant parties to encourage and enable sustained effort to build consensus in advance of CAC45" and "to submit a report two months in advance of CCEXEC83 to inform its further monitoring and critical review, and then to inform further discussion at CAC45".

With respect to science and risk assessment considerations, the two following main issues arose from these consultations:

1. "We heard continuing concerns from Members in two regional informal consultation meetings relating to the lack of MRLs proposed for edible offal other than liver and kidney that were widely consumed locally".
2. "We also heard some concerns regarding establishment of a withdrawal period and the potential for higher chronic intakes of zilpaterol by individuals with high levels of consumption of meat and edible offal from treated animals. Members with these concerns suggested that, in preparation for CAC45, the JECFA secretariat might prepare a simple summary document that explained the basis of the JECFA evaluation of zilpaterol and addressed the concerns raised in this informal consultation process".

In response to these issues, the JECFA Secretariat would like to offer the following responses:

1. JECFA has already evaluated edible offal other than liver and kidney in response to a specific request made by CCVRDF 22[1] to "consider potential zilpaterol hydrochloride residues in animal lungs and other edible offal". This request was addressed by JECFA at its 81st meeting[2] when "The Committee concluded that there were insufficient zilpaterol residue data to adequately consider exposure to residues in lungs and other edible offal of cattle apart from liver and kidney. No non-radio-labelled residue depletion data were provided for any cattle tissues other than liver, kidney and muscle. For lung tissue, there were no actual residue data available in cattle, just estimates based on ratios of plasma versus respiratory tissue radioactivity from preliminary radiolabel studies in rats. For edible offal, the only bovine data available were from a preliminary radiolabel study, with only two data points for tripe at each of the 12- and 48-hour withdrawal periods. Before re-evaluation of zilpaterol with the aim of recommending MRLs in lungs and other edible offal of cattle, the Committee would require marker residue depletion data in such tissues over an appropriate withdrawal period (such as 72 – 96 hours). The Committee noted that the definitions of the tissues comprising offal were not consistent between countries. Therefore, JECFA requests that CCRVDF provides a definition of edible offal

[1] See CCRVDF 22 report https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-730-22%252FREPORT%252FEnglish%252FREP15_RVDFe.pdf

[2] See the residue monograph for zilpaterol prepared by the 81st meeting of JECFA (2015) https://www.fao.org/3/bp390e/bp390e.pdf

before the risk assessment of zilpaterol residues in edible offal can be to be adequately considered by the JECFA".
Since then, the JECFA Secretariat is not aware that sufficient data are available in the public domain that would allow the setting of MRLs for additional tissues, and no Member or Observer has come forward and indicated that such data have become available.

2. Summary of the JECFA evaluation of zilpaterol

ADI and ARfD

The seventy-eighth meeting of JECFA held in 2013 considered the onset of transient and reversible tremors observed in humans, which were consistent with the compound's ß2-adrenergic agonist activity, as the most relevant adverse effect for establishing an acceptable daily intake (ADI) for zilpaterol HCl.

The lowest-observed-adverse-effect level (LOAEL) for tremor was 0.05 mg/person (equal to 0.76 µg/kg bw); the effect was slight at this dose. The Committee established an ADI of 0–0.04 µg/kg bw per day by applying an uncertainty factor of 20, comprising a default uncertainty factor of 10 for human individual variability and an additional uncertainty factor of 2 to account for use of a LOAEL for a slight effect instead of a no-observed-adverse-effect level (NOAEL). The Committee noted that the ADI is based on an acute effect. The Committee also noted that the upper bound of the ADI provides a margin of safety of at least 1250 with respect to the NOAEL of 50 µg/kg bw per day for the formation of leiomyomas (benign tumors) in rats.

The eighty-first meeting of JECFA held in 2015 reaffirmed the ADI of 0–0.04 µg/kg bw that was established at the seventy-eighth meeting of JECFA and established an acute reference dose (ARfD) of 0.04 µg/kg bw based on a LOAEL of 0.76 µg/kg bw for acute pharmacological effects observed in the single-dose human study, with application of an uncertainty factor of 20, comprising a default uncertainty factor of 10 for human individual variability and an additional uncertainty factor of 2 to account for use of a LOAEL for a slight effect instead of a NOAEL.

Full details of the toxicological assessment are provided in the JECFA Toxicological Monograph for zilpaterol: https://www.who.int/publications/i/item/9789241660693.

MRLs

The MRLs recommended for bovine tissues are based on an acute dietary exposure scenario (GEADE). The recommended MRLs for cattle are 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.

Estimated dietary exposure

GEADEs of 1.9 µg/day for the general population and 0.57 µg/day for children were calculated, based on 95/95 Upper Tolerance Levels (UTLs), which represent approximately 80% and 94% of the upper bound of the ARfD for the general population and children, respectively.

Both chronic and acute dietary exposures were considered for residues of zilpaterol. As the ADI and ARfD for zilpaterol are based on an acute pharmacological endpoint, the most relevant approach was deemed the acute exposure assessment. For acute exposure, the GEADE approach was used. Large portion size values based on the 97.5th percentile of food consumption were used in the GEADE assessment of zilpaterol. The consumption amounts used as inputs were based on data from more than 70 consumers to ensure that acute exposure estimates were statistically robust.

The JECFA Secretariat would like to note that the definition of high-level consumers is crucial to the outcome of an acute exposure estimate. The reliability of high percentile consumption data is related to the number of subjects used to calculate them; percentiles calculated on a limited number of subjects should be treated with caution as the results may not be statistically robust. When the number of observations is not large enough, the coverage probability may not attain the nominal value, and drops below, for example, 95%. This is more likely to occur at high percentiles such as the 97.5th. Therefore, the coverage probability can be used to set guidelines to determine the minimum number of samples for which 97.5th percentiles can be computed. In the case of significance level (α) being set at 0.05 to determine a 95% confidence interval, the coverage probability should target 95%. This is achieved for observations where n >70 for the 97.5th percentile. Therefore, a cutoff of n =70 has been used for consumption data used as inputs into acute dietary exposure assessment for zilpaterol HCl.

Full details of the exposure assessment are provided in the JECFA Residue Monograph for zilpaterol (https://www.fao.org/3/I5590E/i5590e.pdf).

Withdrawal periods

JECFA does not establish withdrawal periods but relies on Good Veterinary Practices (GVP) established by Member States. In the case of zilpaterol, where information on authorized uses was provided, withdrawal periods ranged from 2 to 4 days. It is noted that the time point at which the MRLs are calculated (77 hours) is consistent with currently approved withdrawal times (GVP).

In conclusion, we would like to take this opportunity to remind the Membership that during the various discussions on Zilpaterol held at CCRVDF, there was consensus on the risk assessment provided by JECFA – please refer to CCRVDF 24 report[3], in particular para 50 "The Chair, noting that CCRVDF was divided as a committee, not due to concerns regarding science, but for other factors, stated that CCRVDF was not in consensus. He proposed to close the debate for the current session of CCRVDF and not to advance the proposed MRLs. He further noted that CCRVDF did achieve consensus on support for the JECFA evaluation of zilpaterol and the safety of the proposed MRLs, but that CCRVDF was unable to reach consensus on advancing the work in the Step procedure for other reasons".

References:

JECFA 78 Evaluation of certain veterinary drug residues in food (2013)

https://apps.who.int//iris/bitstream/10665/127845/1/9789241209885_eng.pdf

JECFA 81 Evaluation of certain veterinary drug residues in food (2015)

https://apps.who.int/iris/bitstream/10665/204670/1/9789240695504_eng.pdf#page=87

Toxicological evaluation of certain veterinary drug residues in food (2013):

https://www.who.int/publications/i/item/9789241660693

Residue evaluation of certain veterinary drugs (2015):

https://www.fao.org/3/I5590E/i5590e.pdf

[3] See CCRVDF 24 report https://www.fao.org/fao-who-codexalimentarius/sh-proxy/it/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-730-24%252FREPORT%252FREP18_RVDFe.pdf