CODEX ALIMENTARIUS COMMISSION

E

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 3 **CX/RVDF 18/24/3**

December 2017

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-fourth Session

MATTERS OF INTEREST ARISING FROM FAO/WHO AND FROM THE 85TH MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)

Information from the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

1. Since the last session of the CCRVDF, three JECFA meetings (i.e. JECFA 83rd, 84th and 85th) have been convened. These meetings addressed contaminants (JECFA 83rd), food additives (JECFA 84th) and veterinary drug residues (JECFA 85th). The reports and detailed monographs from these meetings are available at the relevant FAO and WHO web sites:

- FAO: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/
- WHO: www.who.int/foodsafety/publications/jecfa/en/

2. JECFA 85th was held in Geneva, Switzerland, from 17 to 26 October 2017 to evaluate residues of certain veterinary drugs in foods. The full report of the meeting is published in the WHO Technical Report Series
(TRS 1008). A fully edited pre-publication report was circulated through the Codex distribution list on December 07 2017.Toxicological monographs summarising the data that were considered by JECFA 85th will be published in *WHO Food Additives Series No.76*[1]; residue monographs summarising the data that were considered by JECFA 85th will be published in *FAO JECFA Monographs No. 21*[2].

3. JECFA 85th recommended Maximum Residues Limits (MRLs) for the following veterinary drugs: amoxicillin (finfish fillet, muscle); ampicillin (finfish fillet, muscle); flumethrin (honey), lufenuron (salmon and trout fillet) and monepantel (cattle fat, kidney, liver, muscle) (CX/RVDF 18/24/6).

4. Furthermore JECFA 85th, noted the following:

Ethion

5. A suitable marker residue could not be determined and an MR:TRR value could not be established. JECFA 85th considered that the residues of concern include the total residues of ethion (i.e. the parent molecule and all metabolites) because the toxicological end-point on which the ADI was set was based on developmental effects, which could not be definitively related to the inhibition of acetylcholine esterase and could not therefore be linked to the known action of ethion monoxon. The metabolites have not been characterized in cattle. As there were several gaps in the available data, and the missing data are essential for setting MRLs, JECFA 85th could not recommend MRLs for ethion at this time.

6. Data needed to complete the assessment, include the following:

a) *Pharmacokinetics and metabolism and residues depletion in cattle:* In order to enable a determination of a suitable marker residue(s), a metabolism study using radiolabelled ethion in cattle is required. The data should be sufficient to determine the ratios of the parent compound and metabolites (i.e. potential marker residues) to the total residues over the residue depletion period in edible tissues (e.g. liver, kidney, muscle and fat), and to identify the metabolites produced. This would also provide information on the relative distribution of the target compounds (parent ethion and/or active metabolites) in the various edible tissues of cattle.

   Cattle metabolites should be compared with the metabolites found in laboratory species to ensure that all residues of toxicological concern produced in cattle have been covered by the available toxicology studies.

[1] http://www.who.int/foodsafety/publications/monographs/en/
[2] http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/

b) *Analytical methods*: Analytical method(s) that can measure suitable marker residues in all edible tissues (e.g. fat, kidney, liver, muscle) should be developed and validated in accordance with established guidance (CXG 71 2009).

Flumethrin

7. Beeswax that originates from a variety of sources may be present in food; because of this, and the fact that flumethrin accumulates in the wax, risk management measures regarding the use of beeswax that may contain residues of flumethrin could be applied. An example is where beekeepers reuse the wax combs season after season in order to maximize honey production. This is common practice, as it takes a lot of energy for the bees to make the wax combs. It might therefore be prudent to advise beekeepers to limit reuse of the combs if they are using products containing flumethrin in their hives. Another measure might be to recommend avoiding using the same active ingredient in subsequent years, but rotating the available products between years. This may also reduce the likelihood of resistance to flumethrin of the target parasites. No data on residues of flumethrin have been evaluated with regard to other products derived from beehives (e.g. propolis, royal jelly, etc.). Therefore, no risk management proposals could be made by JECFA 85th for these commodities.

Halquinol

8. JECFA 85th concluded that a toxicological ADI cannot be established due to the lack of information required to assess the in vivo mutagenicity and carcinogenicity potential of halquinol. MRLs could not be recommended for halquinol due to the lack of an established Health Based Guidance Value (HBGV), incomplete characterization of residues in tissues (particularly liver and kidney) and the lack of data necessary to establish reliable MR:TRR ratios over time for calculation of total residues in tissues.

9. Data needed to complete the assessment, include the following:

- Information to enable the assessment of the in vivo mutagenicity and carcinogenicity potential of halquinol.
- The characterization of specific halquinol metabolites in the radiolabelled study in pigs was incomplete, particularly for liver and kidney samples. Characterization of the non-extractable radiolabelled residues in tissues, as well as the extractable (but not defined) residues, is required.
- Regarding the derivation of MR:TRR ratios over time, JECFA 85th considered the proposed regression approach combining data from the radiolabelled and non-radiolabelled studies to be inappropriate. This was due to a number of factors, including:
    - a greater than 3-fold difference in doses used between the studies (acknowledging that while the pharmacokinetics of halquinol may be linear over this dose range in other species, this has not been demonstrated conclusively in pigs);
    - the discordance of the MR:TRR values derived from the radiolabelled study alone, and the regression approach derived from the combination of radiolabelled/non-radiolabelled data; and
    - the generally low amount of radioactivity observed in swine tissues may cause unacceptable uncertainty in MR and TRR counts.

10. JECFA 85th acknowledged the sponsor's proposal to use the lower bound (more conservative approach) of estimated MR:TRR ratios. However, the total residues are predicted to be the residue of concern. JECFA 85th considered it inappropriate to predict total residues based on potentially unsound MR:TRR estimates, especially in view of the lack of characterization of total metabolite profile in swine tissues noted above.

11. An accurate MR:TRR over the appropriate time in edible pig tissues after halquinol administration should be determined.

12. JECFA 85th noted that new studies may be necessary to address these concerns.

Sisapronil

13. Sisapronil was evaluated by JECFA at the eighty-first meeting when it was not possible to establish an ADI because of potential concerns about effects observed in a 3-month repeated-dose oral toxicity study in dogs. No data were submitted to JECFA 85th, but the sponsor requested further clarification on alternative ways to address the data gaps.

14. There are appreciable differences between rats and dogs in both the toxicokinetics and toxicological effects of sisapronil. Although the half-life of sisapronil was not determined with any accuracy in either species, it is clear that elimination in the dog is much slower than in the rat; while steady state was likely to have been achieved in the rat in the available 1-year repeated-dose oral chronic toxicity study, this was not the case in the dog in the available 3-month study. It would take appreciably longer than 3 months for steady state to be achieved in this species. Although, it has in general been accepted that the repeated-dose oral toxicity of chemicals such as pesticides can be characterized in dogs with only a 3-month study and that there is no need for a 1-year study, this will not be the case for compounds such as sisapronil that take longer than 3 months to reach steady state.

15. The target organs in both rat and dog following repeated-dose oral administration of sisapronil were the liver and the thyroid. Although a mode of action has been established for the thyroid (and liver) effects in rat, this is not the case for the dog. The thyroid effects in the rat are due to induction of hepatic conjugation of thyroid hormones, leading to a reduction in circulating hormone levels, de-repression of thyroid-stimulating hormone synthesis and stimulation of the thyroid gland. In the dog, despite histopathological changes in the thyroid gland, there were no changes in the circulating levels either of thyroid hormones or of thyroid-stimulating hormone. No information was available on the effects of sisapronil on hepatic conjugation of thyroid hormones. Hence, the toxicological significance of the effects on the thyroid in dogs could not be dismissed. In the absence of a study in which steady state levels of sisapronil had been achieved, the long-term potency of sisapronil for these effects could not be characterized.

16. Information on the comparative pharmacokinetics in rats, dogs and humans is not available. In the absence of such information, JECFA made the health-protective assumption that the toxicokinetics of sisapronil in humans might resemble those in dogs. It was not possible for JECFA to interpret the toxicological significance of the findings in the dog in the absence of further information from suitable studies. Hence, JECFA concluded that the findings in dogs should form the basis for the critical NOAEL in the available database for sisapronil but that this hazard has not been adequately characterized.

17. Information that would assist in the further evaluation of sisapronil include:

- Comparative toxicokinetic data in rat, dog and human;
- Effects of sisapronil at steady state following repeated-dose oral administration in the dog; and
- Determination of the relevance of the effects on the thyroid observed in the dog.

Although not all the toxicokinetic data would necessarily have to be generated in vivo, the approach used would have to be suitably validated (e.g. physiologically based toxicokinetic model verified in vivo in rat and dog).

Zilpaterol hydrochloride

18. During the previous zilpaterol assessment, at its 81st meeting, JECFA accounted for limited oral bioavailability of only the non-extractable (bound) zilpaterol residues in cattle tissues. The remaining (extractable) zilpaterol residues were considered to be fully bioavailable. The new bioavailability data submitted to JECFA 85th, support the approach used in the previous assessment. Following evaluation of these data, the MRLs recommended by JECFA at its eighty-first meeting remain unchanged.

General Considerations by JECFA 85th

Chronic dietary exposure assessment of compounds used as veterinary drugs and pesticides

19. Following recommendation of JECFA at its seventy-eighth meeting and of JMPR at the 2015 meeting, an expert working group on the methodology applied by JECFA and JMPR to estimate chronic dietary exposure was convened. The working group was formed to address the issue of how to estimate less-than-lifetime exposure and dietary exposure to residues of substances used as both veterinary drugs and pesticides. For the dual-use exposure assessment, the working group examined two models:

- The global estimate of chronic dietary exposure (GECDE), used by JECFA, for assessing the dietary exposure from veterinary drugs;
- The international estimate of daily intake (IEDI), used by JMPR, for assessing the dietary exposure from pesticide residues.

20. The aim was to develop a practical and scientifically sound harmonized model for estimating total exposure to residues of dual-use chemicals.

21. The working group assessed eight compounds that are used both as pesticides and veterinary drugs and that have been previously evaluated by both JECFA and JMPR: abamectin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, emamectin benzoate, teflubenzuron and thiabendazole. The working group did not examine the toxicological profiles of the compounds to align them with the exposure model for this exercise; it was assumed that less-than-lifetime exposure was a potential concern.

22. A comparison of dietary exposure methodologies was carried out to assess whether:

- Dual uses for the eight compounds resulted in dietary exposure estimates within the relevant ADIs;
- The current JMPR and JECFA dietary exposure methodologies, when applied to dual-use compounds, gave comparable estimates; and
- The current JMPR and JECFA dietary exposure methodologies gave estimates that were sufficiently protective when compared with national estimates of dietary exposure.

23. The median residues estimated by JMPR and JECFA were used to generate three separate sets of dietary exposure estimates. These dietary exposure estimates were:

- IEDI (the JMPR model), based on the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) cluster diets;
- GECDE (the JECFA veterinary drugs model), extended to cover plant products, using the FAO/WHO Chronic individual food consumption database – Summary statistics (CIFOCOss) dataset; and
- National chronic dietary exposure assessments, conducted using food consumption data and national methodologies from Australia, Brazil, the People's Republic of China, the Republic of Korea, the Netherlands, New Zealand and the USA, and from 11 European Union member states, performed by the European Food Safety Authority (EFSA).

24. The estimations were conducted using two different approaches related to the median residues in animal commodities: the highest median residues from JECFA and JMPR, and combined median residues, the sum of the JECFA and JMPR medians.

25. Exposure was estimated in children, adults and the general population as a function of the information available, for median- and high-percentile consumers, to cover less-than-lifetime exposure, where possible. The working group noted that it was not possible to estimate exposure in children or in high-percentile consumers using the JMPR approach.

26. When there are dual-use compounds, residues may be present in animal commodities resulting from the use of the compound as a pesticide and veterinary drug. In this case, the working group assumed that residues will be present in 100% of all animal commodities for both uses. This is consistent with the approaches currently used for the separate assessments of veterinary drugs and pesticides.

27. The results indicate that there were no marked differences between dietary exposure estimates based on the highest median residue or based on the sums of the median residues for the compounds assessed.

28. In principle, the GECDE is a suitable model for the assessment of lifetime and less-than-lifetime dietary exposure. However, the methodology needs to be refined to reflect the improvement of data quality. Consequently, refined GECDE-based dietary exposure estimates are expected to decrease compared with current estimates.

29. The IEDI is suitable for estimating chronic (lifetime) exposure from widely and regularly consumed staple commodities. However, the IEDI is not a suitable model for assessing less-than-lifetime dietary exposure.

30. For the adult population, the IEDI adequately covers the high percentiles obtained by the national estimates for six out of the eight assessed compounds. The GECDE adequately covers the high percentiles obtained by the national estimates for all compounds. It should be noted that in comparison to the IEDI, the GECDE is more conservative for all compounds (up to four times).

31. The IEDI does not specifically address exposure in children. The current IEDI estimates are below the national estimates (high percentiles) for seven out of the eight assessed compounds by a factor of up to four. The GECDE adequately covers the national estimates (high percentiles) for all compounds with a conservativeness of up to four times for the high-percentile group.

32. The working group concluded that, to appropriately link the exposure assessment with the hazard assessment, sensitive populations and relevant exposure duration need to be clearly identified from the toxicological profile for each compound under consideration.

33. The working group made the following recommendations.

In regard to compounds with dual use:

a. JECFA and JMPR are encouraged to always consider dual-use exposure.

b. In the immediate future, residue concentrations obtained from veterinary use and pesticide use in the same animal commodity should be added together to provide the residue data input for the dietary exposure assessment.

c. JECFA and JMPR are encouraged to harmonize their residue definitions to facilitate exposure assessment of dual-use compounds (and subsequently facilitate harmonization of enforcement strategies).

d. The GECDE model should be refined to more accurately encompass national dietary exposure estimates.

In regard to less-than-lifetime exposure:

a. In order to appropriately link the exposure assessment with the hazard assessment, JECFA and JMPR should clearly identify sensitive populations and relevant exposure duration from the toxicological profile for each compound under consideration.

b. JECFA should implement this guidance in future evaluations of food chemicals where appropriate and, after some experience, revise it as appropriate.

c. JMPR should consider the use of individual food consumption data when it is indicated by the toxicological end-points.

In regard to the dietary exposure assessment methodology:

a. The GECDE, subject to further refinement, should be used to assess less-than-lifetime exposure.

b. Exposure to compounds under consideration should be assessed using each individual food consumption survey available in CIFOCOss.

c. The highest reliable percentile rather than the 97.5th percentile should be used for all cases.

In regard to food consumption data collection:

a. FAO and WHO should continue to update the CIFOCOss database to provide a more complete coverage of a broader range of countries and population groups.

b. Wherever possible, FAO and WHO should collect data based on the EFSA Food classification and description system for exposure assessment, revision 2 (FoodEx2 classification). The FoodEx2 classification is more detailed than the Codex classifications, and the mapping with the latter has been done.

c. A conversion table should be developed to approximately translate the foods of animal and plant origin for which food consumption statistics have been collected in CIFOCOss into Raw Agricultural Commodities.

34. JECFA 85th agreed with the conclusions and recommendations of the working group and piloted the combined exposure approach for the two compounds with dual use that were on the JECFA 85th meeting's agenda (i.e. lufenuron and flumethrin). The details and the results of the combined exposure assessment of each compound will be provided as an annex to the relevant JECFA monograph (to be published in 2018).

35. On the basis of the recommendations of the working group, JECFA 85th further considered that the nature of the toxicological effect and the duration of exposure until the onset of effect be addressed as follows:

- Where the ADI is based on a developmental effect, pregnant women will be at potential risk and the critical exposure period may be only a few days or weeks. In such cases, it will be necessary to consider exposure in pregnant high-percentile consumers or an appropriate surrogate population.
- Where the point of departure (POD; e.g. the no-observed-adverse-effect level [NOAEL]) on which the ADI is based is not a developmental effect but is ≤3 times lower than the developmental POD, pregnant women will be at potential risk and the critical exposure period may be only a few days or weeks. In such cases, it will be necessary to consider exposure in pregnant high-percentile consumers or an appropriate surrogate population.

- Where the ADI is based on offspring toxicity, but the POD on which it is based is ≤3 times lower than the POD for long-term toxicity (e.g. 2-year rat study), infants and young children will be at potential risk. In such cases, it will be necessary to consider exposure in infants and young children who are typical (average) consumers.
- Where the POD on which the ADI is based in ≤3 times lower than the POD for offspring toxicity, infants and young children will be at potential risk. In such cases, it will be necessary to consider exposure in infants and young children who are typical (average) consumers.
- Where the ADI is based on offspring toxicity, and the POD on which it is based is >3 times lower than the POD for long-term toxicity (e.g. 2-year rat study), there will be particular concern about the potential risk to infants and young children. In such cases, it will be necessary to consider exposure in infants and young children who are high-percentile consumers.
- Where the ADI is based on effects observed in long-term studies (e.g. 2-year study of toxicity in rats) and the POD in a study (or studies) of shorter duration (e.g. 90-day rat or 90-day dog study of toxicity) is ≤3 times higher than the critical POD (the POD on which the ADI is based), there will be potential concern for less-than-lifetime exposure in the general population. In such cases, it will be necessary to consider exposure in high-percentile adult or general population consumers.

- Where the POD on which an acute reference dose (ARfD) is based is the same as the POD on which the ADI is based, if short-term exposures (children and general population) are not of concern, there will be no concern for less-than-lifetime exposure.
- In all other situations, there will be no specific concerns for less-than-lifetime exposure. In such cases, it will be sufficient to consider exposure in average adult or general population consumers.

Assessment of the relative bioavailability and/or pharmacological activity of incurred drug residues in animal tissues.

36. Recent JECFA assessments and publications have considered the potentially limited oral bioavailability and/or pharmacological activity of incurred drug residues.

37. At the request of CCRVDF21, the limited oral bioavailability of zilpaterol was considered by JECFA as part of its overall evaluation and exposure assessment at the seventy-eighth meeting. Although it was considered that MRLs could not be established at that time due to specific residue depletion data gaps, JECFA did establish an ADI of 0–0.04 µg/kg bw (0–0.00004 mg/kg bw) for zilpaterol. JECFA 81st considered the need to establish an ARfD and concluded that this should be based on the same end-point as the ADI with the same numerical value. Following JECFA 78th's assessment, new data were submitted to JECFA to reassess the bioavailability of incurred zilpaterol residues. If the bioavailability of incurred residues was decreased in relation to oral administration by other routes (e.g. ampoule-containing water administration in humans in fasting condition, the route used in the toxicological study upon which the ADI/ARfD was derived), the human exposure assessments could be further refined.

38. JECFA assesses the bioavailability of non-extractable (i.e. bound) residues based on studies using the Gallo-Torres approach. However, the bioavailability of total (including free or extractable) incurred residues is not routinely considered by JECFA in exposure assessments.

39. JECFA continues to assume, in the absence of evidence to the contrary, that all non-bound incurred residues are equally bioavailable as with other oral dosing regimens, as this provides the most conservative default position. However, JECFA may consider a lower bioavailability of incurred residues in the risk assessment, depending on the strength of evidence available. There is no current guidance on the most appropriate experimental design for studies on the bioavailability of incurred residues. JECFA 85th further considerations on what data may be useful for such an assessment are provided in Appendix I. The guidance is restricted to a consideration of the toxicological implications of systemically available drug residues.

Acute reference dose (ARfD) for residues of veterinary drugs

40. Following a recommendation of JECFA 75th, WHO established a working group to elaborate principles to establish ARfDs for residues of veterinary drugs. Following public consultation, Guidance document for the establishment of Acute Reference Dose (ARfD) for veterinary drug residues in food was published in May 2017 and adopted by WHO at the present meeting[3]. The guidance was first applied in evaluations at the 85th JECFA meeting. The Committee considered whether it was necessary and how to establish an oral acute toxicological and microbiological reference dose for residues of all veterinary drugs evaluated at the meeting. JECFA established ARfDs for amoxicillin, ampicillin, ethion, flumethrin and halquinol

[3] http://www.who.int/entity/foodsafety/chem/jecfa/Guidance-document-ARfD-2017.pdf

Methodological approaches and types of data for assessment of antimicrobial residues in food

WHO list of Critically Important Antimicrobials for Human Medicine

41. JECFA 85th noted ongoing activities of WHO on antimicrobial resistance and the upcoming publication of guidelines on the implications of the WHO list of Critically Important Antimicrobials for Human Medicine[4] (WHO CIA list) for minimizing the emergence and spread of antimicrobial resistance in the food chain. JECFA refers to the WHO CIA list in the "Explanation" section of the evaluation reports on the compounds the Committee evaluates at its meetings.

42. JECFA assesses veterinary drugs with microbiological activity for the potential risk of ingested residues to alter human intestinal microbiota and enhance the emergence of and selection for antimicrobial-resistant bacteria in the gastrointestinal tract. The recommended microbiological acceptable daily intakes (mADIs) set by JECFA ensure that drug residues in animal-derived food are at sufficiently low levels to minimize the potential selection of antibiotic-resistant bacteria in humans. WHO published on the 7th of November 2017 the guidelines on antimicrobial resistance[5]. JECFA will review the guidelines and consider how it might modify its procedures to ensure that the issue of antimicrobial resistance is addressed to the extent possible within its remit.

Microbiological ARfD

43. JECFA 85th adopted the recently published Guidance document for the establishment of Acute Reference Dose (ARfD) for veterinary drug residues in food[6]. The document provides guidance on when and how to establish both a toxicological and a microbiological ARfD. Noted in the Guidance is the distinct difference in the exposure of microorganisms in the gastrointestinal tract following acute intake of microbiologically active drug residues compared with that following chronic daily ingestion. This is addressed by using a dilution factor of 3 in the formula for calculating the microbiological ARfD. The remainder of the formula is the same as that used for calculating the mADI.

44. The formula includes a value for colon volume, which to date has been assumed to be 220 mL (based on mass of colon content of 220 g per day). This value was based on necropsy data of 17 accident victims. In developing the guidance document on establishing ARfDs, the WHO expert working group reviewed more recent studies that used current imaging technology. These studies showed that the hydrated colon of healthy individuals is larger than the 220 g estimate.

45. Pritchard et al. found, using three-dimensional abdominal magnetic resonance imaging techniques, that the 220 g estimate represents approximately the lower 95th percentile of colon volumes among 75 fasting human volunteers. The mean value of 561 mL for the colon volume, based on the combined volumes of the ascending colon, transverse colon and descending colon, provides a more robust estimate. The WHO expert working group noted that this estimate is still low: the measures did not take into account the volume of the lower sigmoid colon because the observations were from fasting individuals.

46. Based on this information, the expert working group concluded that the more appropriate value for the colon volume is 500 mL. This value has therefore been adopted for use in the formulae for calculating the mADI and microbiological ARfD for the evaluation of the effects of antimicrobial residues in food on the intestinal microbiota. JECFA 85th used the new colon volume of 500 mL in the microbiological evaluations of amoxicillin, ampicillin and halquinol.

Approaches for assessment of microbiological activity of veterinary drug residues in food

47. JECFA 85th reviewed the methodological approaches and types of data it receives for assessments of veterinary drug residues in food with regard to their impact on human intestinal microbiota (disruption of the colonization barrier; emergence and selection for antimicrobial-resistant bacteria) with the goal of improving their safety evaluation. In determining mADIs, and now also microbiological ARfDs, JECFA typically:

- Evaluates minimum inhibitory concentration (MIC) data and other in vitro datasets submitted by the sponsor; and
- Reviews the published scientific literature on the susceptibility of selected human intestinal bacteria against antimicrobial agents for the end-point of disruption of the colonization barrier.

[4] http://www.who.int/entity/foodsafety/publications/antimicrobials-fifth/en/index.html

[5] http://www.who.int/entity/foodsafety/publications/cia_guidelines/en/index.html

[6] http://www.who.int/entity/foodsafety/chem/jecfa/Guidance-document-ARfD-2017.pdf

48. The MIC data on the susceptibility to antimicrobial agents of the intestinal microbiota can be very difficult to evaluate because the various laboratories use different procedures and MIC test methods, some of which are not performed according to internationally recognized standards, such as those of the Clinical and Laboratory Standards Institute. In addition, in many cases the number of isolates tested (n < 10) is low, with a lack of MIC distribution information for the isolates. In some cases, the minimum concentrations required to inhibit the growth of 50% of organisms (MIC50) are based on human faecal isolates from clinical infections, not healthy subjects.

49. JECFA recommends that MIC data used to derive mADIs and/or microbiological ARfDs come from studies that use standard internationally recognized methods with at least 10 strains of the relevant genera of intestinal bacteria sourced from faecal samples of healthy donors, as in Step 1 of VICH GL36(R). The selection of intestinal microbiota used in MIC tests should take into consideration recent scientific knowledge from molecular and metagenomic studies on intestinal microbial community composition.

50. In addition, data from in vitro studies (continuous culture flow chemostats) and in vivo models (human volunteers, animal models and human microbiota-associated animals) are evaluated by JECFA for both microbiological end-points. However, data from these studies can be problematic in determining an mADI and/or microbiological ARfD. This is due to the small sample size in the animal studies; insufficient data and low power of studies in human volunteers (because of small numbers of subjects); concentrations of antimicrobial agent generally not being adequate to determine a chronic or acute dose with no effect; and the lack of validation of the in vitro and in vivo test models. In addition, for the antimicrobial resistance end-point, many studies that JECFA evaluates determine the susceptibility and the emergence of resistance only of Escherichia coli and not of the other predominant microorganisms that inhabit the gastrointestinal tract.

51. Therefore, JECFA 85th recommended that in vitro or in vivo studies be conducted using a range of concentrations of the antimicrobial agent, from residue levels to therapeutic levels. Such studies should address the predominant bacterial strains that inhabit the gastrointestinal tract when determining if levels of antimicrobial residues in animal-derived food after consumer ingestion can increase the population of antimicrobial-resistant intestinal bacteria in the gastrointestinal tract.

Characterizing chronic and acute health risks of residues of veterinary drugs in food: latest methodological developments by JECFA

52. The risk assessment of residues of veterinary drugs in food is a field that continues to evolve. The toxicological end-points to be considered are becoming more nuanced and in light of growing concern about the development of antimicrobial resistance, detailed analysis of the antimicrobial activity of the residues of veterinary drugs in food is increasingly incorporated in the assessment. In recent years, JECFA has refined its approaches to provide a more comprehensive and fit-for-purpose risk assessment. A review *"Characterizing chronic and acute health risks of residues of veterinary drugs in food: latest methodological developments by the joint FAO/WHO expert committee on food additives"* recently been published in Critical Review in Toxicology (Crit Rev Toxicol. 2017 Jul 10:1-15)[7], describes in detail the consideration of acute and chronic effects, the estimation of acute and chronic dietary exposure, current approaches for including microbiological endpoints in the risk assessment, and JECFA's considerations for the potential effects of food processing on residues from veterinary drugs. JECFA now applies these approaches in the development of health-based guidance values (i.e. safe exposure levels) for residues of veterinary drugs. JECFA, thus, comprehensively addresses acute and chronic risks by using corresponding estimates for acute and chronic exposure and suitable correction for the limited bioavailability of bound residues by the Gallo-Torres model. On a case-by-case basis, JECFA also considers degradation products that occur from normal food processing of food containing veterinary drug residues. These approaches will continue to be refined to ensure the most scientifically sound basis for the establishment of health-based guidance values for veterinary drug residues.

Global Food Consumption Databases and ongoing activities to support countries to generate and to use data for risk analysis purposes

53. Reliable information on food consumption, collected at individual level, is needed to estimate dietary exposure to chemicals and biological agents in the general population and in vulnerable population groups. To address the issue of insufficient access to such data, FAO and WHO have continued the work on the two following tools (initiated in 2014), to develop global food consumption databases.

- CIFOCOss (FAO/WHO Chronic Individual Food Consumption Data summary statistics) has been further implemented with data from additional countries and available summary statistics are published at http://www.who.int/foodsafety/databases/en/

[7] Open access to the review is available at: http://www.tandfonline.com/doi/full/10.1080/10408444.2017.1340259

- FAO/WHO GIFT (FAO/WHO Global Individual Food consumption data Tool) is the name given to the comprehensive database collating individual quantitative food consumption data for the production of food-based indicators in the field of nutrition, dietary exposure and environmental impact. The dissemination platform was developed based on four datasets. The food categorization system is FoodEx2; it was developed by the European Food Safety Authority (EFSA) and was implemented for use at global level. FAO/WHO GIFT also provides an up-to-date inventory of individual quantitative food consumption surveys conducted and ongoing in low- and middle-income countries, with detailed information on identified studies. The platform is available at http://www.fao.org/gift-individual-food-consumption/en/

54. As part of the ongoing efforts to build national capacity and to populate these databases, a study to improve and harmonize food consumption data in ASEAN countries will be conducted over 2 years starting in May 2016. The project, funded by the EU through the Codex Trust Fund, and technically supported by FAO and WHO, consists of: i) conducting individual food consumption survey in Lao PDR and ii) harmonizing existing data from individual food consumption data in other ASEAN countries in a consistent format. This harmonization activity will consist of:

- Training national teams to perform preliminary categorizing based on the classification of foods using the global categorization system (FoodEx2) developed by the European Food Safety Authority (EFSA);
- The preparation of data in the format needed (variable types, standard codifications, etc.); and
- The ultimate aim is to improve the assessment of nutrient intake and dietary exposure to chemical and biological agents in food (supporting national and international Codex standard-setting).

FAO/WHO activities on antimicrobial resistance (AMR)

FAO

55. In line with the FAO Resolution on AMR and support of the implementation of the Global Action Plan on AMR, FAO is currently supporting the food and agriculture sectors to play their role in addressing the threat posed by AMR. FAO is currently working directly in the food and agriculture sectors with countries in Africa, Asia, Latin America and Eastern Europe and Central Asia to address AMR. Limited awareness and understanding among all stakeholders in the food and agriculture sectors remains a critical barrier to a fully coordinated and effective One Health approach to AMR. FAO is addressing this through collaboration with regional groups and the development of a range of communication and information products. In November 2017, FAO partnered with WHO and OIE to highlight the role of all stakeholders in addressing AMR[8]. Support to the development of One Health National Action Plans remains a priority.

56. To support the food and agriculture sectors in understanding their capacities in relation to AMR susceptibility testing and surveillance, FAO has developed and is applying a tool for the assessment of AMR laboratory capacity and surveillance (ATLASS), the outcomes of which are used as the basis for national level discussions on the establishment of AMR surveillance programmes in the food and agriculture sector. This is being complemented with support to the development of regional strategies for surveillance.

57. FAO is supporting legislative review processes and development or revision of existing legislation at country-level to ensure that the relevant legal instruments are in place to facilitate actions. National legislation relevant to addressing AMR and antimicrobial use are now being tagged in FAOLEX, the largest collection of agriculture relevant legislative instruments.

58. Recognizing that progress on combating AMR will not be achieved without changing practices, is a key focus for FAO activities on AMR. FAO's work in this area is addressing good practices in animal feeding to minimize the need for antimicrobials, Responsible Management of Bacterial Diseases in Aquaculture, good practices in horticulture to minimize the need for antimicrobials and biocide use in food processing. Support is being provided to the adaptation of existing guidance on prudent use and good husbandry practices to local contexts and work is underway to look at the role of agriculture in contaminating the environment with antimicrobial (AM) residues and AMR bacteria.

59. More information on the FAO work on AMR is available at http://www.fao.org/antimicrobial-resistance/en/, and in an overview of activities is available in a paper presented at TFAMR5[9].

WHO

[8] http://www.fao.org/antimicrobial-resistance/world-antibiotic-awareness-week/en/

[9] http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-804-05%252FWD%252Fam05_04e.pdf

60. WHO published the list of Critically Important Antimicrobials for Human Medicine (WHO CIA list) and WHO guidelines on use of medically important antimicrobials in food-producing animals.

- The WHO CIA List provides a ranking of Medically Important Antimicrobials to help prioritize risk management options regarding their use in non-human settings.
- The list was recently updated in 2016 and the most important change in this 5th revision is the new classification of Polymyxins as "highest priority critically important antimicrobials" because of the identification of plasmid-mediated colistin resistance and potential transmission through the food chain.
- The current list and the process/criteria used to establish the list were published in April 2017 and are available online along with its advocacy brochure.[10]
- WHO published, "WHO guidelines on use of medically important antimicrobials in food-producing animals" in November 2017.[11] Building upon two decades of WHO work on containment of antimicrobial resistance (AMR) from the food chain, the aim of these guidelines is to help preserve the effectiveness of medically important antimicrobials, particularly those antimicrobials judged to be critically important for human medicine, in direct support of the global action plan on AMR.[12]
- Full reports from two systematic reviews and the supplemental review, and three literature reviews can be found in the Web Annex A to the guidelines online.[13]

[10] http://www.who.int/foodsafety/publications/antimicrobials-fifth/en/
[11] http://www.who.int/foodsafety/publications/cia_guidelines/en/
[12] http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1
[13] http://apps.who.int/iris/bitstream/10665/259241/1/WHO-NMH-FOS-FZD-17.2-eng.pdf?ua=1

Appendix I

JECFA 85TH CONSIDERATIONS ON THE DESIGN OF INCURRED RESIDUE BIOAVAILABILITY AND PHARMACOLOGICAL ACTIVITY STUDIES

1. Selection of appropriate test animal models

1. There is no validated model established to assess the oral bioavailability of incurred residues, including the most appropriate test animal species (i.e. animals in which the bioavailability of incurred residues will be assessed). The species in which the residues are incurred (i.e. target animal) should be the food animal species for which the veterinary drug is approved (e.g. cattle, swine, poultry, fish).

2. Ideally, a test species with bioavailability comparable to that in humans should be chosen. If it were possible to demonstrate comparable bioavailability of the compound in the test species and in humans (such as by oral tablet, capsule or solution), then this would provide confidence in the extrapolation of the results with incurred residues in the test species to humans.

3. The test animal species in which the bioavailability assessment will be conducted should have a gastrointestinal anatomy and physiology (especially proximal gastrointestinal tract) similar to that of humans. This would include comparable gastrointestinal pH and transit time. The pig is generally considered a suitable animal model to assess bioavailability in humans. However, JECFA noted that other animal models may also be suitable for generating relevant data. For example, although there may be greater difference in proximal gastrointestinal anatomy and transit time between dogs and humans than between pigs and humans (as noted in JECFA 81st's zilpaterol assessment), there remains substantial similarity in gastrointestinal anatomy and physiology between dogs and humans. Incurred residue bioavailability data generated from a dog test system may therefore be considered valid for JECFA's purposes, provided the sponsor includes appropriate justification. One potential reason for using the dog (as opposed to the pig) could be a greater willingness of dogs to ingest the amount of tissue necessary to achieve the desired dose from incurred residues.

2. Dosing strategies for achieving quantifiable tissue and plasma concentrations

4. For some veterinary drugs, it may be difficult to achieve high concentrations of incurred residues in the tissues of the target species (e.g. cattle). In such cases, in order for the test animal (e.g. pig or dog) to ingest a dose sufficient to achieve quantifiable plasma concentrations, it may be necessary to feed appreciable quantities of tissue containing incurred residues.

5. JECFA appreciates that the compound under evaluation may need to be administered to the target species at doses significantly higher than the label dose and the animals killed immediately after the final dose. Killing the target species immediately after the final dose may result in elevated concentrations of drug in plasma, whereas the actual plasma concentrations are likely negligible if the label withdrawal period is followed. This may distort the bioavailability assessment, as it is presumed that residues in plasma may have a higher or lower bioavailability than incurred residues in tissue.

6. Ingestion of a large quantity of tissue at one time by the test species can alter, for example, gastrointestinal motility compared with fasting animals receiving the drug via other oral regimens (e.g. gavage or capsule). Differences in gastrointestinal motility have the potential to alter the timing of residue absorption and thus the maximum concentration (C_{max}).

7. Deviations in drug dosing and withdrawal periods in the target species, and excess tissue ingestion in the test animal, may result in less realistic exposure from incurred residues and a subsequent over- or underestimation of the bioavailability. However, such estimates of bioavailability would provide a useful starting point for subsequent refinement of JECFA's exposure assessment.

3. Pharmacological activity of incurred residues (relay pharmacology)

8. Studies to assess the pharmacological potency of incurred residues (sometimes referred to as "relay pharmacology" studies) assess differences in physiological or pharmacological end-points in the test animal after administration of the drug via incurred residues compared with other oral administration methods (e.g. gavage, capsule or dietary admixture). Studies to determine the relative bioavailability of incurred residues ("bioavailability" studies) measure the plasma concentrations after ingestion of the drug via incurred residues and other oral administration methods, and derive the relevant pharmacokinetic parameters (C_{max} and area under the concentration–time curve [AUC]) from such data. In the former, all the pharmacologically active substances present contribute to the response measured; in the latter, only the parent compound is typically assessed.

9. Bioavailability and relay pharmacology are obviously related. In fact, a single study could assess both the relative bioavailability (pharmacokinetics) of incurred residues compared with other oral administration methods and the pharmacological activity (pharmacodynamics) observed after the various oral doses are administered. Such a combination study may not be feasible in all cases due to technical challenges (e.g. collecting blood samples without biasing clinical end-points determined at the same time). However, the ability to integrate the pharmacokinetic and pharmacodynamic data (PK/PD modelling) would enable a clear relationship between the drug residues in plasma and their actual effect.

10. For example, although the pharmacokinetic parameter AUC is traditionally used for assessing bioavailability (drug exposure), the Committee considers that for some compounds having short reversible drug–receptor interactions, the magnitude of relevant effect may correlate more closely with the parameter C_{max} than with AUC.

4. Other issues regarding the assessment of relative bioavailability and relay pharmacology

11. As with any clinical study, the necessary sample size for a relative bioavailability or relay pharmacology study will depend on the magnitude of the expected differences between groups, as well as the degree of variance. For relative bioavailability or relay pharmacology studies, a crossover design with appropriate wash-out period (similar to bioequivalence studies) may be used to increase the study power and minimize the required sample size. Sponsors are encouraged to refer to Guideline 52 of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH GL52) for further details regarding appropriate sample sizes and timing of plasma collection.

12. Relative oral bioavailability studies may not be feasible for incurred drug residues comprising multiple components (e.g. parent compound + metabolites). In order to determine the relative bioavailability of each incurred residue component, the concentrations of each component must be quantified in both the incurred tissue residues and the test animal plasma.

13. The doses used in a relay pharmacology study should be consistent with those known to cause a predictable pharmacological response in the test animal species. The primary outcomes measured should be a result of discrete pharmacological activity. Such outcomes should also be quantifiable, simple to measure and not persist for prolonged durations. Examples of appropriate outcome measure include changes in heart rate, blood pressure, respiration or motor activity.

14. If different oral bioavailability and/or pharmacological activities for incurred residues are claimed, supporting data can be provided for all the animal-derived tissues that significantly impact the human exposure assessment. For tissues for which data on bioavailability / relay pharmacology of incurred residues are not available, JECFA will assume the same bioavailability / pharmacological activity as by direct oral exposure.