Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Eighty-fifth meeting (Residues of veterinary drugs)
Geneva, 17–26 October 2017

SUMMARY AND CONCLUSIONS

Issued 9 November 2017

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 17 to 26 October 2017. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Mr J. Schefferlie, Veterinary Medicinal Products Unit, Medicines Evaluation Board Agency, Utrecht, the Netherlands, served as Chairperson, and Dr L. Friedlander, United States Food and Drug Administration, Rockville, Maryland, USA, served as Vice-Chairperson.

Dr P. Verger, Department of Food Safety and Zoonoses, World Health Organization, and Dr M. Lipp, Food Safety and Quality Unit, Office for Food Safety, Food and Agriculture Organization of the United Nations, served as Joint Secretaries.

The present meeting was the eighty-fifth in a series of similar meetings and the twenty-third JECFA meeting specifically convened to consider residues of veterinary drugs in food. The tasks before the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food, for establishing acceptable daily intakes (ADIs) and acute reference doses (ARfDs) and for recommending maximum residue limits (MRLs) for such residues when the drugs under consideration are administered to food-producing animals in accordance with good practice in the use of veterinary drugs (GVP); to evaluate the safety of residues of certain veterinary drugs; and to respond to specific concerns raised by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). In total, eight veterinary drugs were evaluated by the Committee.

The report of the meeting will be printed in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, comments on specific substances and recommendations. The report will include an annex (similar to Annex 1 in this summary) summarizing the conclusions reached by the Committee relating to ADIs, dietary exposure and MRLs.

Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 2. Future work and recommendations arising from the meeting are summarized in Annex 3. The participants are listed in Annex 4.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series No. 76. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monographs No. 21.

More information on the work of JECFA is available at:

http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/

and

http://www.who.int/foodsafety/en/

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Annex 1

Recommendations on the substances on the agenda

Amoxicillin (antimicrobial agent)

Acceptable daily intake	The Committee established a microbiological ADI (mADI) of 0–0.002 mg/kg body weight (bw) based on the effects of amoxicillin on the intestinal microbiota.
Acute reference dose	The Committee established an ARfD of 0.005 mg/kg bw based on microbiological effects on the intestinal microbiota.
Estimated chronic dietary exposure	The global estimate of chronic dietary exposure (GECDE) for the general population is 0.14 µg/kg bw per day, which represents 7% of the upper bound of the mADI.
Estimated acute dietary exposure	The global estimate of acute dietary exposure (GEADE) for the general population is 1.4 µg/kg bw, which represents 28% of the microbiological ARfD.
	The GEADE for children is 1.6 µg/kg bw, which represents 31% of the microbiological ARfD.
Residue definition	Amoxicillin

Recommended maximum residue limits (MRLs)

Species	Fillet[a] (µg/kg)	Muscle (µg/kg)
Finfish[b]	50	50

[a] Muscle plus skin in natural proportion.

[b] The term "finfish" includes all fish species.

Ampicillin (antimicrobial agent)

Acceptable daily intake	The Committee established an overall mADI of 0–0.003 mg/kg bw based on a no-observed-adverse-effect level (NOAEL)

	equivalent to 0.025 mg/kg bw per day for increase in population(s) of ampicillin-resistant bacteria in the gastrointestinal tract in humans, and using a safety factor of 10 (for the variability in the composition of the intestinal microbiota within and between individuals).
Acute reference dose	The Committee established an ARfD of 0.012 mg/kg bw based on the microbiological end-point.
Estimated chronic dietary exposure	The GECDE for the general population is 0.29 µg/kg bw per day, which represents 10% of the upper bound of the ADI.
Estimated acute dietary exposure	The GEADE for the general population is 1.9 µg/kg bw per day, which represents 16% of the ARfD. The GEADE for children is 1.7 µg/kg bw per day, which represents 14% of the ARfD.
Residue definition	Ampicillin
Maximum residue limits	The Committee recommended an MRL of 50 µg/kg for ampicillin in finfish muscle and in finfish muscle plus skin in natural proportion, the same as that recommended for amoxicillin, because the modes of action, the physicochemical properties and the toxicological and pharmacokinetic profiles of amoxicillin and ampicillin are very similar.

Ethion (acaricide)

Acceptable daily intake	The Committee established an ADI of 0–0.002 mg/kg bw based on the NOAEL of 0.2 mg/kg bw per day for embryotoxic effects in a rat developmental toxicity study, and using a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee established an ARfD of 0.02 mg/kg bw based on the NOAEL of 0.15 mg/kg bw for erythrocyte acetylcholinesterase inhibition in a repeated-dose human study, and using an intraspecies safety factor of 10.
Estimated dietary exposure	No dietary exposure assessment could be conducted.
Residue definition	None. A suitable marker residue could not be determined and a marker to total residue ratio could not be established.
Maximum residue limits	The Committee was unable to recommend MRLs for ethion.

Flumethrin (type II pyrethroid insecticide)

Acceptable daily intake	The Committee established an ADI of 0–0.004 mg/kg bw based on the NOAEL of 0.37 mg/kg bw per day for skin lesions in parental animals and reduced survival and body-weight gain in

	pups in a two-generation toxicity study in rats, and using a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee established an ARfD of 0.005 mg/kg bw based on the NOAEL of 0.5 mg/kg bw for salivation in dams in a developmental toxicity study in rats, and using a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Estimated chronic dietary exposure	As Flumethrin is also used as pesticide the overall dietary exposure was estimated. The assumptions and detailed results will be displayed in the JECFA 85 report. Results below are only for use as veterinary drug. The GECDE for the general population is 0.008 µg/kg bw per day, which represents 0.2% of the upper bound of the ADI. The GECDE for children is 0.006 µg/kg bw per day, which represents 0.2% of the upper bound of the ADI.
Estimated acute dietary exposure	The GEADE for the general population is 0.1 µg/kg bw per day, which represents 2.2% of the ARfD. The GEADE for children is 0.1 µg/kg bw per day, which represents 2.2% of the ARfD.
Residue definition	Flumethrin (trans-Z1 and trans Z2 diastereomers at a ratio of approximately 60:40).
Maximum residue limits	The Committee set an MRL for honey of 6 µg/kg, which is twice the limit of quantification (LOQ; 3 µg/kg) of the most reliable analytical method (liquid chromatography coupled with tandem mass spectrometry; LC–MS/MS) used in the residues studies.

Halquinol (broad spectrum antimicrobial)

Acceptable daily intake	In the absence of information required to assess the in vivo mutagenicity and carcinogenicity potential of halquinol, the Committee was unable to establish an ADI for halquinol. An mADI of 0–0.3 mg/kg bw was derived from in vitro MIC susceptibility testing data.
Acute reference dose	A microbiological ARfD of 0.9 mg/kg bw was established based on the effects of halquinol on the intestinal microbiota.
Estimated dietary exposure	No dietary exposure assessment could be conducted.
Residue definition	None due to incomplete characterization of residues in tissues.
Maximum residue limits	The Committee was unable to recommend MRLs for halquinol.

Lufenuron (insecticide)

Acceptable daily intake	The Committee established an ADI of 0–0.02 mg/kg bw based on the NOAEL of 1.93 mg/kg bw per day for tonic-clonic seizures and findings in lungs, gastrointestinal tract, liver and urinary tract in a 2-year dietary study in rats, and using a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee concluded that it was unnecessary to establish an ARfD for lufenuron in view of its low acute oral toxicity and the absence of developmental toxicity and other toxicological effects likely to be elicited by a single dose.
Estimated chronic dietary exposure	As Lufenuron is also used as pesticide the overall dietary exposure was estimated. The assumptions and detailed results will be displayed in the JECFA 85 report. Results below are only for use as veterinary drug. The GECDE for the general population is 1.1 µg/kg bw per day, which represents 5.5% of the upper bound of the ADI.
Residue definition	Lufenuron

Recommended maximum residue limits (MRLs)

Species	Fillet[a] (µg/kg)
Salmon	1 350
Trout	1 350

[a] Muscle plus skin in natural proportion.

Monepantel (anthelminthic)

Acceptable daily intake	The ADI of 0–0.02 mg/kg bw per day established by the Committee at the seventy- fifth meeting (WHO TRS No. 969, 2012) remains unchanged.
Acute reference dose	The Committee concluded that it was unnecessary to establish an ARfD.
Estimated chronic dietary exposure	The GECDE for the general population is 13.7 µg per kg bw per day, which represents 68% of the upper bound of the ADI. The GECDE for children is 5.0 µg per kg bw per day, which represents 25% of the upper bound of the ADI. The GECDE for infants is 4.4 µg per kg bw per day, which represents 22% of the upper bound of the ADI.
Residue definition	Monepantel sulfone

Recommended maximum residue limits (MRLs)[a]

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	7 000	1 000	2 000	300

[a] Determined as monepantel sulfone, expressed as monepantel.

Zilpaterol hydrochloride (β_2-adrenoceptor agonist)

Following evaluation of the bioavailability data submitted, the MRLs recommended by the Committee at its eighty-first meeting (WHO TRS No. 997, 2016) remain unchanged.

Sisapronil (ectoparasiticide)

No additional data were submitted. As a result, the ADI remains unestablished.

Annex 2

General considerations

An edited version of this section will be included in the report of the eighty-fifth meeting of JECFA. It is reproduced here so that the information can be disseminated quickly.

Matters of interest arising from previous sessions of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)

The Twenty-third Session of CCRVDF has agreed:

- to initiate discussion on the feasibility of establishing MRLs for groups of fish species for veterinary drugs; on providing a definition for "edible offal"; and on specifying edible offal tissues of interest in international;
- to add information on the registration of a compound as a pesticide and, where applicable, information on the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) evaluation to the form requesting information on compounds for evaluation by JECFA. This form is attached to the Circular Letter requesting proposals for inclusion in the Priority List for veterinary drugs requiring evaluation or re-evaluation by JECFA;
- to request FAO and WHO scientific advice on whether veterinary drugs residues in food commodities resulting from the carry-over of drug residues into feed constitutes a human health risk and which recommendations could be established to address the trade issues while protecting human health;
- on a Priority List of veterinary drugs for evaluation (or re-evaluation) by JECFA. CCRVDF discussed at some length the difficulty in identifying data to support the evaluation of veterinary drugs by JECFA.

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

An expert working group on the methodology applied by JECFA and JMPR to estimate chronic dietary exposure was convened to develop a practical and scientifically sound harmonized model for estimating total exposure to residues of dual-use chemicals.

The working group compared the dietary exposure methodologies of eight previously evaluated compounds (abamectin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, emamectin benzoate, teflubenzuron and thiabendazole) 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 to national estimates of dietary exposure.

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

- international estimate of daily intake (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 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, the USA, and from 11 European Union member states performed by the European Food Safety Authority (EFSA).

The estimates 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. The results indicate that there were no marked differences between these two approaches.

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.

The following recommendations were made:

In regard to compounds with dual use:

1. JECFA and JMPR are encouraged to always consider dual-use exposure.
2. 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.
3. 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).
4. The GECDE model should be refined to more accurately encompass national dietary exposure estimates.

In regard to less-than-lifetime exposure:

1. 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.
2. JECFA recommends this guidance be implemented in future evaluations of food chemicals where appropriate and, after some experience, be revised as appropriate.
3. 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:

1. The GECDE, subject to further refinement, should be used to assess less-than-lifetime exposure.
2. The compounds under consideration should be assessed using each individual food consumption survey available in CIFOCOss.
3. The highest reliable percentile should be used rather than the 97.5th percentile for all cases.

In regard to food consumption data collection:

1. FAO and WHO continue to update the CIFOCOss database to provide a more complete coverage of a broader range of countries and population groups.
2. Wherever possible, FAO and WHO collect data based on the more detailed EFSA FoodEx2 classification and description system, which is more detailed than the Codex classifications.
3. A conversion table is 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.

The Committee piloted the combined exposure approach for lufenuron and flumethrin at the present meeting.

On the basis of the recommendations of the working group, the Committee 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. 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 a 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 ARfD 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 tissue

JECFA assesses the bioavailability of non-extractable (i.e. bound) residues based on studies using the Gallo-Torres approach (Gallo-Torres, J Toxicol Environ Health. 1977;2:827–45). However, the bioavailability of total (including free or extractable) incurred residues is not routinely considered by JECFA in exposure assessments.

The Committee continues to assume that all non-bound incurred residues are equally bioavailable as with other oral dosing regimens, as this provides the most conservative default position. However, the Committee 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.

Further considerations on what data may be useful for such an assessment is restricted to the toxicological implications of systemically available drug residues:

1. Selection of appropriate test animal models

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

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.

The test animal species should have a similar gastrointestinal anatomy and physiology (especially proximal gastrointestinal tract) as 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, the Committee noted that other animal models may also be suitable for generating relevant data. For example, although there may be greater differences in proximal gastrointestinal anatomy and transit time between dogs and humans than between pigs and humans, there is substantial similarity in gastrointestinal anatomy and physiology of 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

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.

The Committee 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 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.

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}).

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)

Studies for assessing the pharmacological potency of incurred residues ("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.

Bioavailability and relay pharmacology are obviously related. In fact, a single study could assess both the relative bioavailability (pharmacokinetics) of incurred residues compared to other oral administration methods as well as 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.

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

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

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 washout 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 International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products Guideline (VICH GL 52 (Bioequivalence, VICH 2015) for further details regarding appropriate sample sizes and timing of plasma collection.

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.

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.

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, the Committee will assume the same bioavailability / pharmacological activity as by direct oral exposure.

ARfD for residues of veterinary drugs

Following a recommendation of the Committee at its seventy-fifth meeting (WHO TRS No. 969, 2012), WHO established a working group to elaborate principles to establish ARfDs for residues of veterinary drugs. Following public consultation, the *Guidance document for the establishment of Acute Reference Dose (ARfD) for veterinary drug residues in food* was adopted by the WHO and published in May 2017. The guidance was first applied by JECFA in evaluations at the present (eighty-fifth) 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. ARfDs were established for amoxicillin, ampicillin, ethion, flumethrin and halquinol.

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

The *Guidance document for the establishment of Acute Reference Dose (ARfD) for veterinary drug residues in food* (FAO/WHO, 2017) 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.

The formula includes a value for colon volume, to date assumed to be 220 mL (based on mass of colon content of 220 g per day). In developing the guidance on establishing ARfDs, studies that used current imaging technology were reviewed. These studies showed that 500 mL was the more appropriate value for the colon volume, and this volume 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. At the present meeting, the new colon volume was used in the microbiological evaluations of amoxicillin, ampicillin and halquinol.

The Committee 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, and emergence and selection for antimicrobial-resistant bacteria) with the goal of improving their safety evaluation. In determining mADIs and microbiological ARfDs, the Committee typically:

- evaluates minimum inhibitory concentration (MIC) data and other in vitro datasets submitted by the sponsor;
- 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.

The MIC data on the susceptibility to antimicrobial agents of the intestinal microbiota can be very difficult to evaluate: various laboratories use different MIC test methods and some tests are not performed according to internationally recognized standards; in many cases the number of isolates tested 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 (MIC_{50}) values are based on faecal isolates from clinical infection cases and not healthy subjects.

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 the Committee for both microbiological end-points. However, these studies can be problematic due to the small sample sizes in the animal studies; insufficient data and low power of studies in human volunteer studies; inadequate concentrations of antimicrobial agent used to determine a chronic or acute dose with no effect; and lack of validation of the in vitro and in vivo test models. In addition, many studies determine the susceptibility and the emergence of resistance only of *Escherichia coli* and not of the other predominant microorganisms that inhabit the gastrointestinal tract.

The Committee recommends:

- that, for meaningful interpretation of MIC data, studies be conducted according to internationally recognized standards using at least 10 strains of the relevant genera of intestinal bacteria sourced from faecal samples of healthy donors (as in Step 1 of VICH Guideline 36(R); VICH, 2010);
- taking into consideration recent scientific knowledge from molecular and metagenomic studies on intestinal microbial community composition; and
- that in vitro or in vivo studies be conducted using a range of concentrations of the antimicrobial agent, from residue levels to therapeutic levels, and that these studies address the effects on the predominant bacterial strains that inhabit the gastrointestinal tract.

Annex 3

Future work and recommendations

Ethion

Information essential in the evaluation of the compound

- In order to determine suitable marker residue(s), a metabolism study using radiolabelled ethion in cattle is required
    - 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, fat), and
    - to identify the metabolites.
- Cattle metabolites should be compared with laboratory species metabolites to ensure that all residues of toxicological concern produced in cattle have been covered by the available toxicology studies.
- Analytical method(s) that can measure suitable marker residues in all edible tissues should be developed and validated in accordance with established guidance (CAC/GL71-2009).
- As the ADI for ethion was based on developmental effects and is 10-fold lower than the ARfD, specific exposure scenarios are required to address exposure in high-percentile pregnant consumers or a suitable surrogate population. This exposure scenario will also be protective of children.

Halquinol

Further information required to complete the residue assessment:

- Characterization of the non-extractable radiolabelled residues in tissues as well as the extractable (but not defined) residues;
- An accurate marker residue to total radioactive residue (MR:TRR) ratio over the appropriate time in pig edible tissues; and
- Further characterization of halquinol metabolites in tissues.

Sisapronil

Further information that would assist in the further evaluation of the compound

- 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 dogs.

Although not all the toxicokinetic data on sisapronil would 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).

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

The following recommendations were made:
In regard to compounds with dual use:

1 JECFA and JMPR are encouraged to always consider dual-use exposure.
2 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.

3 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).
4 The GECDE model should be refined to more accurately encompass national dietary exposure estimates.

In regard to less-than-lifetime exposure:

1. To appropriately link the exposure assessment with the hazard assessment, JECFA and JMPR should clearly identify sensitive populations and relevant exposure durations from the toxicological profile for each compound under consideration.
2. JECFA recommends this guidance be implemented in future evaluations of food chemicals where appropriate and, after some experience, be revised as appropriate.
3. 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:

1. The GECDE, subject to further refinement, should be used to assess less-than-lifetime exposure.
2. The compounds under consideration should be assessed using each individual food consumption survey available in CIFOCOss.
3. The highest reliable percentile should be used rather than the 97.5th percentile for all cases.

In regard to food consumption data collection:

1. FAO and WHO continue to update the CIFOCOss database to provide a more complete coverage of a broader range of countries and population groups.
2. Wherever possible, FAO and WHO collect data based on the more detailed EFSA FoodEx2 classification and description system, which is more detailed than the Codex classifications.
3. A conversion table is 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.

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

The Committee recommends:

- that, for meaningful interpretation of MIC data, studies be conducted according to internationally recognized standards using at least 10 strains of the relevant genera of intestinal bacteria sourced from faecal samples of healthy donors (as in Step 1 of VICH Guideline 36(R); VICH, 2010);
- taking into consideration recent scientific knowledge from molecular and metagenomic studies on intestinal microbial community composition; and
- that in vitro or in vivo studies be conducted using a range of concentrations of the antimicrobial agent, from residue levels to therapeutic levels, and that these studies address the effects on the predominant bacterial strains that inhabit the gastrointestinal tract.

Annex 4

Eighty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Geneva, Switzerland, 17–26 October 2017

WHO Members

Professor Alan R. Boobis, Centre for Pharmacology & Therapeutics, Department of Experimental Medicine, Division of Medicine, Faculty of Medicine, Imperial College London, London, United Kingdom

Dr Carl E. Cerniglia, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Department of Health and Human Services, Jefferson, Arkansas, United States of America (USA)

Dr Daniel R. Doerge, Division of Biochemical Toxicology, National Center for Toxicological Research, Food and Drug Administration, Department of Health and Human Services, Jefferson, Arkansas, USA

Professor Sang-Hee Jeong, Department of Biomedical Science, College of Life and Health Science, Hoseo University, Asan City, Chungnam, Republic of Korea

Dr Utz Mueller, Australian Pesticides and Veterinary Medicines Authority, Kingston, Australian Capital Territory, Australia

Professor Emeritus Leonard Ritter, University of Guelph, Guelph, Ontario, Canada (*WHO Rapporteur*)

Mr Johan Schefferlie, Veterinary Medicinal Products Unit, Medicines Evaluation Board Agency, Utrecht, the Netherlands (*Chairperson*)

Temporary advisers

Dr Cecilia Aguila, Toxicology Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, Maryland, USA

Dr Bitte Aspenström-Fagerlund, Department of Risk and Benefit Assessment, Division of Science, National Food Agency, Uppsala, Sweden

Professor Silvana Lima Górniak, Department of Pathology, School of Veterinary Medicine and Animal Sciences, University of São Paulo, São Paulo, Brazil

Dr Kumiko Ogawa, Division of Pathology, Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan

Dr Chris Schyvens, Scientific Assessment and Chemical Review, Australian Pesticides and Veterinary Medicines Authority, Kingston, Australian Capital Territory, Australia

FAO Members

Dr Joe O. Boison, Canadian Food Inspection Agency, Government of Canada, Saskatoon, Saskatchewan, Canada

Mr Peter Cressey, Institute of Environmental Science and Research Limited (ESR), Christchurch Science Centre, Christchurch, New Zealand

Dr Lynn G. Friedlander, Residue Chemistry Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, Maryland, USA (*Vice-Chairperson*)

Professor Susanne Rath, Department of Analytical Chemistry, University of Campinas, Campinas, São Paulo, Brazil

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FAO Experts

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Dr Silvia Piñeiro, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, Maryland, USA[1]

Secretariat

Ms Annamaria Bruno, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the UN, Rome, Italy (*Senior Food Standards Officer, Codex Secretariat*)

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[1] Unable to attend the meeting.